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FACTORS FAVORING SUCCESSFUL TRANSMETATARSAL AMPUTATION IN DIABETES*

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ALTHOUGH the emergency character of infectious or early gangrenous lesions of the toes and feet of diabetic patients has long been recognized by most physicians, a new aspect of this problem is presented by the demonstration that in many diabetic patients a useful and serviceable foot can be preserved through the proper use of the transmetatarsal amputation.[1, 2] Actually, in the last two years major amputations above the ankle have become less frequent at the New England Deaconess Hospital (Table 1). The danger inherent in minor lesions and the importance of teaching all older diabetic patients simple prophylactic measures appeared time and time again in the records of these 920 patients, many of whom cut a corn or drew blood by trimming a callus and walked on the foot for weeks before going to a physician for attention. Mildness of the diabetes is no protection against gangrene and, if overemphasized by the physician, gives the patient a false sense of security. Gangrene characteristically occurs in the obese, neglected diabetic patient with low insulin requirements and little or no glycosuria but with a malignant tendency to arteriosclerosis in the legs, the coronary vessels and the retinas. The injunction not to walk on a sore toe must be endlessly repeated: the insensitive foot is most dangerous and least resistant to infection.

The introduction of chemotherapy, especially penicillin, made possible control of infection to such a degree as to improve the possibility of carrying out with success conservative surgical procedures in diabetic patients. The group of patients so far operated upon have been selected with such attention to details that success has been obtained in 6 out of 7 operations. The analysis of the various factors making for success or failure in this group includes estimation of the blood supply, determination of the infection present and assessment of such factors as the duration and type of the diabetes and presence or absence of cardiac and renal complications.

It became evident early in this series that the line separating failure and success was extremely narrow. In some patients successful healing occurred when the chances seemed remote. It was particularly true that certain patients who failed to heal promptly in the hospital did, after a prolonged period at home, succeed in obtaining a thorough healing and useful foot. This paper summarizes some of the clinical data in an attempt to present criteria for the selection of patients for operation.

TABLE 1. *Types of Diabetic Amputation in 920 Cases at the New England Deaconess Hospital.*

OPERATION	NO. OF CASES 1942–1945	1946–1947
Major amputation	269	84
Transmetatarsal amputation	56	95
Transmetatarsal amputation followed by thigh amputation	(11)	(14)
Toe amputation	322	94
Totals	647	273

CLINICAL MATERIAL

One hundred and thirty-three transmetatarsal amputations were carried out on 122 different diabetic patients in the New England Deaconess Hospital between 1944 and September, 1947, by Drs. Leland S. McKittrick, John B. McKittrick, Norman L. Wilson, Theodore C. Pratt and Clifford C. Franseen. In 22 cases failure to heal is recorded, but in 3 of these, thigh amputation was not necessary. In 1 case after a period of many months at home healing finally occurred, and in 2 cases the result was termed a failure because of recurrence of ulcerations in anesthetic feet. The remaining 19 cases that failed to heal necessitated a subsequent thigh amputation.

The failures occurred chiefly in women, numbering 17 as against 5 failures in men. This preponderance is in excess of the proportion of women in the series since there were 74 female as against 59 male patients, in the total of 133 operations. This proportion is consistent with the sex incidence of

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diabetes in middle and later life, although the sex incidence is equal in childhood diabetes.

The duration of the diabetes must be considered at the same time as the age of patients at the time of operation. Thus, the duration was greatest in the 2 men operated upon in the fourth decade, both of whom had adequate blood supply to the foot but suffered typical neurogenic anesthetic feet. The bulk of the operations were done in patients being between fifty-one and eighty years of age, totaling 52 out of 59 in men and 69 out of 74 in women. The duration of diabetes in these patients varied from nine years in the men between fifty-one and sixty years of age and fifteen years in the women between seventy-one and eighty years of age. The average duration of diabetes was ten years in the successful operations and fourteen years in the failures. It is evident that long duration of diabetes does not contraindicate this operation, although in general the longer the duration of diabetes in the patients in the older groups, the more serious the risk. The average age in the successful operations was sixty-one years, and in the failures it was sixty-five years (Table 2).

TABLE 2. *Age and Duration of Diabetes at Time of Transmetatarsal Amputation.*

AGE	MALE PATIENTS		FEMALE PATIENTS	
	NO.	DURATION OF DIABETES	NO.	DURATION OF DIABETES
yr.		yr.		yr.
31–40 ...	2	17	0	0
41–50 ...	4	13	3	14
51–60 ...	16 (2)*	9	26 (4)	9
61–70 ...	26 (2)	10	30 (8)	14
71–80 ...	10 (1)	11	13 (5)	15
81–90 ...	1	0.2	2	6
Totals .	59		74	

*Figures in parentheses indicate failure to heal.

NATURE OF LESIONS

In this group, gangrene of one or more toes was present in 78 cases. In these 78 cases the pathological report also mentioned osteomyelitis. In another 19 cases osteomyelitis alone was recorded. In 36 cases the lesions were described as chronic ulcerations in the feet, with defective circulation or with neurotrophic disturbance of sensation. In all cases some type of trauma had been present. Often the trauma was slight, consisting merely of the pricking of a blister that had broken or the cutting of a corn, and the commonest lesion was the infected callus with extension into the bone or joint. The lesions were described as localized or invasive according to the presence of lymphangitis or evidence of acute extending infection at the time of admission. It should be said that in this diabetic group practically all the lesions were invasive in the sense that the extension of infection from an infected corn or callus to a bone or joint with osteomyelitis, which is common in the diabetic patient, is rare in the person without the disease. To this extent it is a peculiarly invasive lesion. However, unless the lesion was accompanied by active extending invasive infection at the time of admission, it was considered to be localized. The invasive lesions numbered 62, and the localized lesions 71. In many cases in which lymphangitis or infection extended above the ankle the use of penicillin resulted in the subsidence of infection in the favorable cases to a degree that permitted the transmetatarsal amputation. The relation of invasive infection to successful operation is shown by the fact that successful operations were done in 50 cases of invasive infection. In the failures invasive infection was present in 12 out of 22 cases. In the cases of localized infection success was obtained in 61, and failure occurred in 10. It is evident therefore that success was not dependent upon the presence or the lack of the active invasive type of infection.

NATURE OF DIABETES

This group of patients stands out as composed of mild cases of diabetes of long duration in patients who had formerly been extremely obese. Table 3 shows groups of the patients classified according to maximum weight. In 22 operations the maximum weight of the patient had been between 225 and 315 pounds, with an average of 245 pounds. The average maximum weight had been 208 pounds in 52 cases and 170 pounds in 50 cases. In only 4 cases had the maximum weight been less than 150 pounds. The loss of weight up to the time of the operation averaged in these different groups from 75 down to 19 pounds. The average period between the maximum weight and the time of operation showed very little variation in the different groups.

TABLE 3. *Obesity and Weight Loss.*

MAXIMUM WEIGHT	NUMBER OF CASES	AVERAGE MAXIMUM WEIGHT	AVERAGE WEIGHT AT OPERATION	AVERAGE WEIGHT LOSS	AVERAGE PERIOD OF WEIGHT LOSS	DURATION OF DIABETES AT OPERATION
lb.		lb.	lb.	lb.	yr.	yr.
315–225	22	245	171	75	15	11.0
224–190	52	208	147	59	17	8.5
189–150	50	170	136	34	18	13.2
Under 150	4	138	117	19	16	10.5
No data	5	—	—	—	—	—

It is evident that serious foot lesions in mild diabetic patients depend in part upon an antecedent obesity and in part upon metabolic changes associated with great losses of weight due in large measure to relatively uncontrolled diabetes. The preceding treatment of diabetes in the group had as a whole been haphazard. Thus, in the successful cases, 99 patients had had no measured diet, and 21 patients among the failures had similarly had no measured diet. Actually only 13 patients in the series had been on a measured diet, and in those the period of a measured diet had been only a small part of the diabetic history. In the successful amputations insulin had been administered on the average for six years and seven months in 82 cases, and in 14 cases in this group insulin had been used for less than six months. In 15 of the successful operations no insulin had ever been used. Among the failures 20 patients out of the 22 had been taking insulin for an average of eight years and nine months. In this group two cases had taken no insulin. The striking factor here is the comparatively long period during which diabetes had existed without treatment by means of insulin. More important, however, is the fact that even though insulin had been used, the balance of diet and insulin had not been successfully or accurately maintained, with the result that glycosuria and hyperglycemia not only were present at admission but also had probably been present long before the recurrence and development of the lesion that brought about admission to the hospital.

Circulation

The condition of the circulation, both general and local, is undoubtedly in many cases a chief factor in determining success. In the successful patients the blood pressure on admission averaged 167 systolic, 84 diastolic, whereas in the failures the value was 166 systolic, 84 diastolic. During the period of convalescence the average minimal blood pressure in the successful cases was 120 systolic, 76 diastolic, whereas in the failures the average minimal pressure was 133 systolic, 77 diastolic. Although in both groups patients showed slightly high blood pressures, the series as a whole was characterized by moderate hypertension of the systolic type, which naturally fell during rest more in the successful group than in the failures.

One might therefore suppose that a slightly greater degree of systemic hypertension was present in the failures. However, the local circulatory conditions undoubtedly were more important than the systemic blood-pressure readings. In the estimation of local circulation, presence or absence of normal palpable pulsations in the dorsalis pedis, popliteal and posterior tibial arteries was considered of chief importance. However, the appearance of the foot regarding atrophy of muscles on the affected side, the normally rapid or slow filling of the veins after emptying, the development of rubor upon hanging the foot down, the presence of thin, shiny skin with loss of subcutaneous weight and the temperature of the foot and leg measured by palpation were taken into account. In the successful patients pulsation in the dorsalis pedis artery was absent in 76 and present in 35 cases, whereas in the failures pulsation in the dorsalis pedis was absent in 21 cases. Almost the same situation was true of the pulsation in the posterior tibial artery. Pulsation of the popliteal artery is notoriously difficult to record with accuracy. A slight change in position of the patient makes the pulse easily felt one day and absent to palpation on another. However, among the successful cases the pulse was present in 91 and absent or not felt in 20 cases. It was absent in 6 of the 22 failures. If one single evidence of the character of peripheral circulation were to be relied upon the presence or absence of pulses in the dorsalis pedis vessel would probably be of greatest service provided that palpation were carried out with care and deliberation on more than one occasion and provided due allowance was made for the difficulty of feeling pulsation in a foot swollen with edema and inflammation.

In summary one may say that a deficient blood supply as indicated by absent pulsation in the dorsalis pedis, posterior tibial and popliteal arteries was a conspicuous feature in the cases in which failure occurred, and yet exception occurred in which healing proceeded successfully in spite of apparently hopelessly deficient circulation, so that some other factor must be assumed (Table 4). This factor may be humoral or in the tissue. It may be nutritional, or it may be concerned with the mechanism by which infection is controlled.

Infection

Cultures were made from the open lesions in 92 cases. *Staphylococcus aureus* was the most important single organism, but the combination of *Staph. aureus* and a streptococcus occurred in 21 cases among the successful amputations and in 4 cases among the failures.

Hemolytic streptococcus alone was obtained in 7 cases. The hemolytic *Staph. aureus* was obtained in 20 cases, and the *Staph. aureus* in 21 cases. Other organisms such as diphtheroids, enterococcus, *Streptococcus faecalis* and *Clostridium welchii* (1 case) were reported in 16 cases. Seven of the 22 failures showed *Staph. aureus*, 1 hemolytic *Staph. aureus*, 3 hemolytic streptococcus and 4 a mixture of staphylococcus and streptococcus.

Unfortunately, no division of the *Staph. aureus* was carried out, but it is evident that this species, in combination with other organisms, is at present the most frequent organism found in cultures obtained from open wounds. As yet no definite information is available whether the organisms are derived from outside sources or have been

carried to the lesion from within the patient's own body. The presumption is that they gain entrance into the tissue through injury and break in the skin, and that, once the skin is broken, the poor local resistance of the diabetic tissue enables the organisms to invade muscle, soft tissue and finally bone and joint spaces. The nature of the defect that makes diabetic patients so vulnerable to invasive infection by these organisms is a matter of speculation. For many years repeated studies have failed to disclose in the blood or body fluids a mechanism directly related to the staphylococcus. In animals made diabetic the study of staphylococcal lesions is not easy because many animals do not develop staphylococcal infections in a manner comparable with that of human beings. It seems more likely that the resistance to such organisms is a matter of tissue resistance rather than a humoral mechanism. Patients with diabetes of long duration are well known to show a variety of tissue changes, which are measurable both by pathological technics and by clinical methods. It is also well known that normal glycogen may be greatly reduced in content in diabetic acidosis as well as in states of diabetic malnutrition. Although the level of glucose may increase in normal tissue and in the skin of diabetic patients not under good control, at the same time the glycogen content of the diabetic skin is greatly reduced. The concentration of glycogen is directly affected and increased when adequate insulin and dietary treatment is carried out. Similar changes in the lipoid content of diabetic tissues — notably, liver, kidneys and nerve tissues — have been recorded. An increase in the lipoid content of the blood except the cholesterol content occurs under conditions of diabetic maladjustment, particularly when there has been a great loss of weight and tissue cachexia. Recently, the relation of vitamins and the disturbances of nutrition associated with avitaminosis has been intensively studied, and particularly in experimental diabetes attention has been given to the effect of thiamine chloride deficiency. As yet, however, no clear picture of the mechanism by which diabetic tissues lose the power of resisting invasion by the staphylococcus and streptococcus has been presented.

Anesthetic Feet

Other factors in this group of patients may be emphasized. In 24 of the successful cases various degrees of anesthesia of the toes, foot or even of the lower leg were present, whereas in 2 of the failures this factor was prominent. Deficient sensation in diabetic feet has been a matter of clinical observation for many years. It is associated with the loss of reflexes and sometimes with changes in the central nervous system indicated by an increase of protein in the cerebrospinal fluid. The importance of the finding of anesthesia lies in the fact that these feet healed readily after surgery and will remain healed so long as the patient is in bed or spending only a short period on his feet. Continued use of the feet in walking results sooner or later in pressure areas, ulcerations and infection, and the resistance to infection of this group of patients seems even lower than that in the group as a whole. Frequently associated with this anesthesia, which usually is not accompanied by any serious impairment of blood supply, there may be an increase in the protein of the cerebrospinal fluid and a well marked increase in capillary fragility. In this group the spinal-fluid protein was above 50 mg. per 100

TABLE 4. *Factors Affecting 133 Transmetatarsal Amputations among 122 Diabetic Patients.*

Result of Operation	No. of Cases	Patients Taking Insulin for More than 6 Mo.	Patients Taking Insulin for Less than 6 Mo.	Patients Not Taking Insulin	Duration of Diabetes	Average Age	Average Blood Pressure	
							on admission	after rest
					yr.	yr.		
Success	111	82	14	15	10	61	164/84	120/76
Failure	22	18	2	2	14	65	166/84	136/77

TABLE 4 (*Continued*).

Result of Operation	No. of Cases	Cases of Invasive Infection	Cases of Localized Infection	Patients with Hemoglobin above 14 Gm.	Patients with Hemoglobin below 14 Gm.	Patients with *Staph. aureus* Infection	Patients with Hemolytic *Staph. aureus* Infection	Patients with Staphylococcal and Streptococcal Infection
Success	111	50	61	41	70	14	19	21
Failure	22	12	10	9	13	7	1	4

cc. in 24 of the successful cases and 5 of the failures. It was below 50 mg. in 18 successful cases and 4 failures. Albuminuria, hypertension and retinitis were common. In 36 of the successful cases and 12 of the failures hemorrhages and exudates were present in the eyegrounds. Serious impairment of vision was common. However, in 37 cases hemorrhages and exudates were not noted although it must be said that in many of these cases the examinations were not carried out by an ophthalmologist.

Previous Lesions

In 51 patients of this series there had been previous infections of the streptococcus and staphylococcus type, including ulcerations, carbuncles and boils. In 56 cases amputations of a toe or in a few cases of a leg had previously been performed. This group, therefore, consisted of patients in whom by and large the arteriosclerotic process had been in evidence for a considerable period, and the amputation through the transmetatarsal area was in many cases done as a matter of desperation to save one foot when the other had already been amputated. The frequency of these infections suggests again the well known fact that, although in the course of healing one assumes that local immunity has developed and antibodies occur, not only is there no persisting immunity but also these patients seem to represent a group in which a specific vulnerability to the organisms continues. As a practical consequence the teaching given to diabetic patients should emphasize all precautions, not merely directed against trauma but particularly designed to prevent and control infections whenever any break of the skin has permitted the entry of the organisms.

This group is often described as made up of patients with mild diabetes. If one takes as evidence of mildness the amount of insulin required and glycosuria present, this statement may be true. Actually, in this group the average maximum insulin dosage was 31 units for successful cases and 48 units for the failures, and at discharge, after a prolonged period of hospital treatment, the average was 17 units for the successful cases and 24 units for the failures. One may say, therefore, that the failures represented a somewhat severer type of diabetes; however, even this conclusion is not safe since the difference in the insulin dosage is slight and readily accounted for on the basis of more serious infection in the cases of failure. The important point, however, is to recognize the fact that the severity of diabetes in this group of patients is not to be measured by the glycosuria or the requirement of insulin dosage. Actually, a better measure is some assessment of the effect of diabetes in producing loss of weight, malnutrition, vascular disease, impairment of nerve supply and, finally and most important of all, the destruction of the normal resistance against invasive infection by the staphylococcus and the streptococcus.

Follow-up Study

A follow-up summary to April, 1948, of all patients undergoing transmetatarsal amputations at the New England Deaconess Hospital is presented in Table 5. The striking improvement in the selection of patients is shown by the fact that in 1944 and 1945, 45 out of 56 operations were successful, 10 failed to heal and required thigh amputations and 1 patient died of coronary occlusion. In the second period, 1946-1947, only 14 failures

Table 4 (*Continued*).

Blood Sugar			Average Glycosuria on Admission	Average Albumin in Urine	Average Amount of Insulin in Hospital		Patients with Measured Diet	Patients with Unmeasured Diet	Average Diet at Discharge	
on admission	maximum	on discharge			maximum	on discharge			carbohydrate	
mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*%*	*mg.*	*units*	*units*			*gm.*	*cal.*
178	239	131	1.5	92	31	17	12	99	164	1764
183	266	142	1.9	93	48	24	1	21	159	1652

Table 4 (*Continued*).

Patients with Pulsation in Dorsalis Pedis Artery	Patients with No Pulsation in Dorsalis Pedis Artery	Patients with No Pulsation in Posterior Tibial Artery	Patients with No Pulsation in Popliteal Artery	Patients with Anesthetic Feet	Patients with Spinal-Fluid Protein above 50 Mg. per 100 Cc.	Patients with Retinitis	Patients without Retinitis
35	76	73	20	24	24	36	33
1	21	21	6	2	5	12	4

occurred in 95 operations, and in 1948 only 1 unsuccessful operation was performed in 19. A single postoperative death occurred in the total of 170 operations.

Examination of the patients or a doctor's report in 1948 revealed that of the 45 patients who left the hospital in 1944 and 1945 with a healed transmetatarsal amputation 30 are still healed and walking, 4 walk with some limitation, 5 of the patients who required thigh amputation in 1944 and 1945 are walking with a prosthetic appliance, and the other 5 are included among the 12 patients who died of coronary occlusion and other vascular complications after discharge from the hospital. In the period 1946-1947 out of 81 successful operations 70 patients are still healed and walking, 5 more have limited walking, 14 who suffered a thigh amputation are still walking with a prosthetic appliance and 3 are dead. One of the most striking facts is that in only 2 cases out of 144 patients who left the hospital with a healed transmetatarsal amputation has a subsequent thigh amputation become necessary on the same side. In these cases trauma to the leg led to gangrene at the level of the ankle in 1 and at the level of the shin in the other. The deficiency of the blood supply was so great that thigh amputation followed. However, if the patient once succeeds in healing a transmetatarsal amputation the foot is a useful foot and stands the strain of walking for a long time.

TABLE 5. *Results of Follow-up Study in 170 Transmetatarsal Amputations.*

PERIOD	TOTAL OPERATIONS	SUCCESSFUL OPERATIONS	UNSUCCESSFUL OPERATIONS*	DEATH OF PATIENTS	CONDITION OF PATIENT AT LAST EXAMINATION†					
					PATIENTS HEALED AND WALKING	PATIENTS WITH LIMITED WALKING	PATIENTS WALKING WITH PROSTHETIC APPLIANCE	PATIENTS WITH IPSOLATERAL THIGH AMPUTATIONS	DEATHS FROM CORONARY OCCLUSION AND OTHER COMPLICATIONS	NO DATA AVAILABLE
1944–1945	56	45	10	1	30	4	5	—	12	4
1946–1947	95	81	14	—	70	5	14	2	3	1
January–April, 1948	19	18	1	—	18	—	1	—	—	—

*Followed by thigh amputation.
†1948.

Failure to heal occurred in 22 of the amputations, and 19 patients required subsequent thigh amputation (failures occurred chiefly among female patients). In all cases trauma, usually slight, was followed by gangrene. Most of the patients had mild diabetes and had once been overweight. The blood pressures among the failures were higher than those among the successful cases.

Results have steadily improved since 1944, owing to selection of patients and the introduction of chemotherapy and penicillin.

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SUMMARY

An analysis of 133 transmetatarsal amputations in 122 cases of diabetes at the New England Deaconess Hospital is presented. The danger of infections or early gangrene resulting from cutting of corns or trimming of callus among diabetic patients is stressed. All persons with diabetes should be constantly warned against walking on a sore toe.

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BRONCHIAL ADENOMA*

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BRONCHIAL adenoma was first recognized sixty-five years ago, and yet it received little mention in the literature until relatively recently. Since the publication of Reisner's[1] article in 1928 several excellent clinical and pathological descriptions of this tumor have been written. The increasing awareness of bronchial adenoma has led to its more frequent recognition and to a more thorough understanding of the altered respiratory physiology and of the pulmonary complications to which it predisposes. The recent advances in thoracic surgery have broadened the therapeutic approach to these tumors, as well as to other types of pulmonary lesions. The purpose of this communication is to review the literature and to present our experience with bronchial adenoma.

The incidence of bronchial adenoma has been stated to be approximately 6 per cent of all primary bronchial tumors.[2] It comprised 12 per cent of 278 neoplasms diagnosed bronchoscopically by Clerf and Bucher.[3] Of 217 histologically proved primary lung tumors encountered at the Lahey Clinic since 1930, 15 were bronchial adenomas, an incidence of 6.9 per cent. Adams[4] has discussed some of these cases in a previous report. It is of interest to note that the diagnosis has been confirmed in 9 cases during the past three years, whereas only 6 cases of bronchial adenoma were discovered over the preceding fifteen years. For ease of description the cases have been numbered in the order in which they were diagnosed, and the pertinent features of each are summarized in Table 1.

The origin of bronchial adenoma remains unsettled. It appears that most adenomas arise in the submucosa of the bronchial wall, probably from the bronchial glands or ducts. From this point of origin growth progresses into the bronchial lumen as well as extrabronchially. Brunn and Goldman[5] stated that extrabronchial extension occurs in 90 per cent of cases; however, this was definitely found in only 7 of the cases.

Because of the uncertain origin and variable morphology of these tumors, numerous terms have been suggested for bronchial adenoma. Nevertheless, it is believed that the use of this designation is desirable until the situation is clarified.

With few exceptions bronchial adenomas are situated in a primary bronchus, where they can be readily visualized through the bronchoscope. In the 15 cases reported herein, the tumor was seen by the bronchoscopist in 12. In Case 8 the growth was in a segmental bronchus of the left upper lobe, where it could not be demonstrated. In Case 13 there was definite narrowing of the right-lower-lobe bronchus from external pressure without evidence of intrabronchial growth. At operation the latter was found to arise in the dorsal division of the right-lower-lobe bronchus and to possess an extrabronchial portion several times larger than that within the lumen. In Case 5 bronchoscopy was not performed.

When seen bronchoscopically an adenoma appears as a rounded, pink or reddish-purple mass, the surface of which is often bosselated. The tumors are usually attached by a broad base but rarely have a distinct pedicle that permits the entire mass to move with respiration or instrumentation (Case 3). Not infrequently blood vessels can be seen on the surface of the tumor. As a rule, there is no visible ulceration. Adenomas are notorious for profuse bleeding following manipulation, and death has been reported from aspiration of blood after biopsy.[6] Instrumentation did not cause serious bleeding in any of our cases.

If an adenoma is satisfactorily visualized, its distinctive appearance usually differentiates it from carcinoma. Whereas carcinoma often produces fixation of the bronchus, this almost never occurs in the presence of adenoma. Carcinomas are frequently ulcerated, and although they may bleed freely at biopsy, this is seldom troublesome. Microscopical examination of biopsy material is essential in the differential diagnosis but is not without its shortcomings. In the first place, the forceps may not penetrate the tumor deeply enough to obtain characteristic cells, and secondly, squamous metaplasia of the surface epithelium or distortion of the cells may lead to an erroneous diagnosis of carcinoma. Serial sections minimize the possibility of error.

Histologically, bronchial adenomas have been divided into two main types: carcinoid and mixed tumor, or cylindroma. The latter is considered by some investigators to possess greater malignant potentialities than the more common carcinoid type.[7, 8] Womak and Graham[9] prefer the term "mixed tumor" for all adenomas because of their resemblance to mixed tumors of the salivary glands and the occasional presence of bone and cartilage. The cellular structure of the carcinoid type is comparable to that of appendiceal carcinoids, parathyroid adenomas and basal-cell carcinoma.[10]

Differences of opinion regarding the potential malignancy of bronchial adenoma have interfered with the adoption of uniform therapy. Foster-

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Carter,[11] Jackson et al.[12] and Clerf and Bucher[3] concluded that the tumors are essentially benign. On the other hand, Wessler and Rabin[13] found evidence of malignancy in 2 cases. Adams, Steiner and Bloch[14] reported 5 cases, 2 with distant metastases, which they considered to be malignant. Metastasis to the liver has been described by Anderson[15] and by Holley.[16] Laff and Neubuerger[7] found malignant change with spread to the opposite lung thirteen years after the original diagnosis of cylindroma. Lymph-node involvement was present in 5 of 10 cases reported by Chamberlain and Gordon.[17]

TABLE 1. *Summary of Cases.*

Case No.	Sex	Age	Duration	Symptoms	Physical Findings	Roentgenologic Findings	Bronchoscopic Findings
1	F	33	4 yr.	Cough, sputum hemoptysis, recurrent fever, sweats and pleurisy	Diminished breath sounds; rales over right lower lobe.	Atelectasis, right lower lobe; no filling of dorsal division, right-lower-lobe bronchus, on bronchography.	Tumor mass, right-lower-lobe bronchus.
2	F	34	1 yr.	Cough, hemoptysis and chest discomfort	Negative	Soft-tissue mass, lower pole of right hilus	Tumor mass, right-lower-lobe bronchus.
3	F	23	2½ yr.	Cough, wheeze, chest discomfort, chills, fever and weight loss	Diminished breath sounds, right lower and middle lobes; increased breath sounds, right upper lobe.	Obstructive emphysema, right lung	Right main bronchus almost completely occluded by pedunculated tumor, which could be moved 1 cm.; brisk bleeding.
4	M	30	6 yr.	Cough, sputum, pressure in chest and hemoptysis	Diminished breath sounds over right lower lobe	Soft-tissue mass, right hilus	Tumor mass in right-lower-lobe bronchus; active bleeding on biopsy.
5	F	38	5 yr.	Cough, sputum; pneumonia three times.	Negative	Infiltration and bronchiectasis, right lower lobe; bronchogram done.	No bronchoscopy done
6	M	59	6 yr.	Cough, sputum, hemoptysis; repeated pneumonia.	Diminished resonance and breath sounds, left lower lobe	Atelectasis and bronchiectasis, left lower lobe	Tumor mass obstructing left-lower-lobe bronchus
7	M	41	2 yr.	Vague abdominal distress and hemoptysis	Negative	Questionable mass, right hilus	Tumor mass at junction of right-middle and lower-lobe bronchi
8	F	29	2½ yr.	Cough, dyspnea and chest discomfort	Inspiratory lag on left	Tumor and segmental atelectasis; bronchiectasis, left upper lobe.	No tumor seen
9	F	51	8 mo.	Repeated hemoptyses	Negative	Mass, right hilus; partial atelectasis, right lower lobe.	Tumor mass within right-lower-lobe bronchus extending into middle-lobe bronchus
10	M	42	3 yr.	Cough and repeated hemoptyses	Negative	Negative	Pedunculated tumor, right main bronchus encroaching upon carina
11	M	13	1 yr.	Cough, wheeze, dyspnea, chest discomfort; repeated pneumonia, and weight loss.	Diminished breath sounds and resonance, left lower lobe	Atelectasis, left lower lobe	Tumor, left main bronchus
12	M	37	16 mo.	Cough, hemoptysis and chest discomfort	Negative	Infiltration, midportion of left lung field	Tumor, left-upper-lobe bronchus extending to lower-lobe bronchus
13	F	49	4 yr.	Cough, sputum, pleurisy and severe hemoptysis	Diminished breath sounds and resonance, right lower lobe	Tumor mass, right hilus; atelectasis, right lower lobe.	Narrowing of right-lower-lobe bronchus from external pressure; no tumor visible within bronchus.
14	F	47	18 mo.	Cough, purulent sputum, hemoptysis, repeated pneumonia and weight loss	Diminished breath sounds and resonance, left lower lobe	Atelectasis, left lower lobe	Tumor obstructing left-lower-lobe bronchus and extending into upper-lobe bronchus
15	M	32	8 mo.	Cough, sputum, wheeze, dyspnea; severe hemoptysis once.	Wheeze over left lower lobe when patient was lying on left side; rhonchi.	Negative	Tumor mass arising in left main bronchus, extending into upper-lobe bronchus and almost completely filling lower-lobe bronchus

Graham and Womack[18] believe that some adenomas become malignant with loss of their original identity. Local infiltration by tumor cells has been with tumor cells present in two hilar lymph nodes."

From these facts one must conclude that bronchial adenoma is a potentially malignant neoplasm.

TABLE 1 (*Continued*).

CASE No.	TREATMENT	PATHOLOGY	RESULTS OF FOLLOW-UP STUDY	COMMENT
1	Local removal and electrocoagulation twice; removal of right lower and middle lobes.	Carcinoid type, with invasion and infiltration of wall; large extrabronchial portion; bronchiectasis.	Patient well 6½ yr. after lobectomy	Despite repeated examinations and removal of recurrent growth, pressure from extrabronchial portion led to bronchostenosis and bronchiectasis
2	X-ray therapy; local removal and electrocoagulation.	Infiltrating, carcinoid type	Patient well after 6½ yr.	—
3	Local removal; electrocoagulation of base.	Infiltrating, carcinoid type	Patient well after 4½ yr.	—
4	Removal of right middle and lower lobe	Low-grade adenocarcinoma arising from adenoma, with involvement of 2 hilar lymph nodes	Patient well after 4 yr.	Seropositive congenital syphilis present
5	Removal of right lower lobe	Infiltrating, carcinoid type, at orifice of right-lower-lobe bronchus, with large extrabronchial extension; bronchiectasis.	Patient well after 2½ yr.	Diagnosis not made preoperatively
6	Removal of left lower lobe	Infiltrating, carcinoid type; bronchiectasis.	Patient well after 2 yr.	—
7	Removal of right middle and lower lobes	Infiltrating, carcinoid type, with ossification of stroma	Patient well after 2 yr.	—
8	Removal of left upper lobe	Tumor in segmental bronchus, left upper lobe; carcinoid type; bronchiectasis.	Patient well after 20 mo.	—
9	Removal of right middle and lower lobes	Infiltrating, carcinoid type	Patient well after 14 mo.	—
10	Local removal and electrocoagulation, twice	Infiltrating, carcinoid type	Patient well after 7 mo.	—
11	Partial removal; pneumonectomy (left) elsewhere.	Infiltrating, carcinoid type	No follow-up study	—
12	Recurrence 2 months after local removal and electrocoagulation; pneumonectomy (left).	Infiltrating, carcinoid type, with ossification of stroma	Dysphagia after 5 mo.	Pressure on esophagus by bronchial stump
13	Removal of right, middle and lower lobes	Tumor, dorsal division of right-lower-lobe bronchus infiltrating, carcinoid type, with large extrabronchial extension	Patient well after 6 mo.	Immediate operation because of severe hemoptysis
14	Removal of left lung	Infiltrating, carcinoid type; bronchiectasis, left lower lobe.	Patient well after 5 mo.	—
15	Removal of left lung	Infiltrating, carcinoid type	—	Patient operated on too recently for follow-up observations

a frequent finding, and was detected in 14 cases. In Case 4 the pathological diagnosis was "low-grade adenocarcinoma arising from bronchial adenoma The grade of malignancy is apparently low, inasmuch as there are no cases on record in which death has resulted from sudden rapid growth of the tumor

with widespread metastases — a common finding in the usual type of bronchiogenic carcinoma.

Clinical Considerations

Age and Sex

Adenoma of the bronchus is largely a disease of the younger age groups. Sixty per cent of the 15 patients were under 40 years of age, the converse of the age distribution of bronchiogenic carcinoma.

Table 2. *Age and Sex Distribution.*

Age	No. of Patients	Female Patients	Male Patients
yr.			
11–20	1	0	1
21–30	3	2	1
31–40	5	3	2
41–50	4	2	2
51–59	2	1	1
Average age		38.0	36.3

The age range was from 13 to 59 years, with an average of 37.15 years (Table 2). Eight patients (53 per cent) were women.

Duration of Symptoms

It is not uncommon to discover bronchial adenoma as the cause of respiratory symptoms of several years' standing. The duration of symptoms among these patients varied from 8 months to 6 years, with an average of 2.7 years. This parallels the experience of others.

Symptoms

Cough and sputum. Cough, the commonest symptom of bronchial adenoma, was the initial symptom in 7 and was present in 13 patients. At the outset the cough is likely to be mild, but with growth of the tumor the bronchial irritation increases and the cough becomes more distressing. This symptom may be most troublesome at night or when the patient assumes a particular position. The presence of sputum depends largely upon the degree of bronchial obstruction produced by the adenoma. Early, therefore, sputum may be absent or mucoid in character owing to the increased bronchial secretion. When bronchial obstruction and infection supervene, with or without actual bronchiectasis or abscess, the sputum tends to become purulent. Sputum was present to some degree in 8 of the patients in this series.

Hemoptysis. Hemoptysis is one of the outstanding manifestations of adenoma of the bronchus. It occurred one or more times in 11 of the 15 patients; in 3 it was the initial symptom. In Case 13 hemoptysis was of such severity and persistence as to necessitate prompt surgical intervention. Typically, the bleeding is sudden in onset, brisk and fairly abrupt in cessation. In the female patients hemoptysis was not related to the menses. It seems likely that in most cases bleeding results from the rupture of a blood vessel on the surface of the adenoma since, as mentioned above, the tumors are almost never found to be ulcerated. The presence of bronchiectasis constitutes another possible source of hemorrhage.

Wheeze. Wheeze was an outstanding complaint of 3 patients, 2 of whom were referred to the clinic with a presumptive diagnosis of bronchial asthma. One extremely important feature of the wheeze accompanying bronchial adenoma is its tendency to be localized to a definite area. In addition, it may be transient and vary with change of position; this is especially true of the pedunculated adenoma as exemplified by Case 3. Wheeze tends to disappear as the bronchus becomes completely obstructed.

Dyspnea. Although as a rule not extreme, dyspnea may be distinctly troublesome. This complaint was present in 4 cases. Moderate diminution of vital capacity may result from atelectasis or obstructive emphysema. If the latter is of sufficient degree to produce mediastinal shift, the function of the sound lung will be compromised. Dyspnea is often more pronounced with partial than with complete bronchial obstruction.

Chest discomfort. Varying degrees of chest discomfort occur fairly frequently in association with bronchial adenoma. In general, this is mild and is often described as a feeling of fullness or pressure in the chest. The most severe type of pain encountered is due to pleuritis. Six patients complained of mild chest pain.

Pulmonary infection. Patients with bronchial adenoma are prone to develop pulmonary sepsis. Often there is a history of recurrent bouts of pneumonia involving the same lobe, or of slowly resolving pneumonia. Bronchial obstruction may, in addition to producing pneumonitis, lead to bronchiectasis or abscess formation. In other cases the clues to the underlying process are less obvious, the clinical manifestations being limited to fever, either intermittent or continuous, sweats and, not infrequently, weight loss. Four patients had recurrent episodes of pneumonia. Two others had repeated chills and fever. Pleurisy was present in 2 cases. Three patients lost from 12 to 25 pounds in weight.

Physical Findings

Abnormal findings on physical examination are in direct proportion to the degree of bronchial obstruction and the extent of pulmonary involvement distal to the tumor. In the presence of partial obstruction of a bronchus decreased resonance and distant breath sounds, with or without wheeze, may be detected over the involved lobe. Rales or rhonchi will be added in the presence of pneumonitis or bronchiectasis. Obstructive emphysema develops distal to adenomas that permit ingress of air but occlude the bronchus during expiration. With complete bronchial obstruction the findings are those

of atelectasis. There may be a noticeable disparity in the size and expansion of the two hemithoraces. Compensatory emphysema of the uninvolved lobes is not uncommon in cases with complete occlusion of the bronchus. The fact that in 6 patients physical examination of the chest was negative serves to emphasize the fact that abnormal physical signs are not essential to a diagnosis of bronchial adenoma.

Roentgenologic Findings

Roentgenograms of the chest reveal abnormalities in the majority of cases of adenoma of the bronchus; however, special technics are frequently necessary to establish a reasonably exact diagnosis. Most observers have mentioned atelectasis as the most common finding, followed by inflammatory infiltration, a visible tumor mass and obstructive emphysema. It must be emphasized that none of these findings are diagnostic of bronchial adenoma. Whether present singly or in combination, they indicate nothing more than mechanical interference with normal bronchial function. The visible tumor mass produced by an adenoma cannot be differentiated from other types of bronchial tumors by roentgenologic study alone. Final diagnosis must rest upon the bronchoscopic and histopathological appearance.

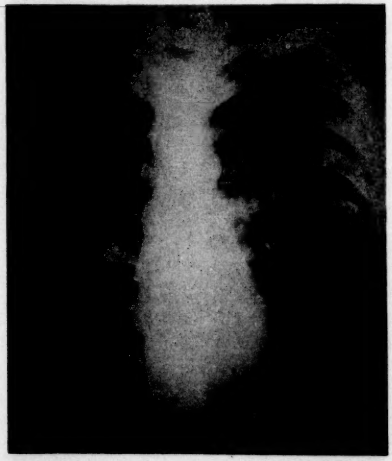

Figure 1. *Plain Film in Case 4, Showing a Rounded Soft-Tissue Mass at the Lower Pole of the Right Hilus.*

Atelectasis alone was demonstrated in 3 cases, a tumor mass (Fig. 1) in 3, inflammatory infiltration (Fig. 2) or bronchiectasis in 2 and various combinations of these findings in 4 cases (Fig. 3 and 4). Obstructive emphysema was present in 1 patient (Fig. 5). Chest roentgenograms were normal in 2 cases. Overexposed (grid or Bucky) films are valuable in detecting intraluminal tumors, which, as a rule, are less readily discernible than extrabronchial

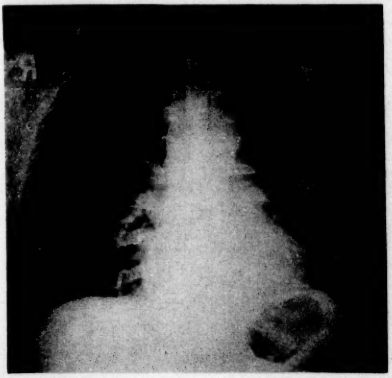

Figure 2. *Inflammatory Infiltration of the Midportion of the Left-Lung Field in Case 12.*

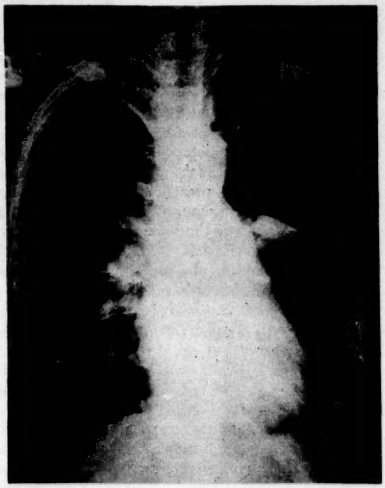

Figure 3. *Tumor Mass, Segmental Atelectasis and Bronchiectasis of the Left Upper Lobe in Case 8.*
The adenoma was not visualized at bronchoscopy.

masses. Fluoroscopy and roentgenograms taken during forced expiration aid in discovering obstructive emphysema and should therefore be utilized whenever partial bronchial obstruction is suspected. Body-section roentgenography, as advocated by Lowry and Rigler,[2] has not been employed in this clinic.

Bronchography occasionally proves of value and was employed in 2 cases. The chief indications for

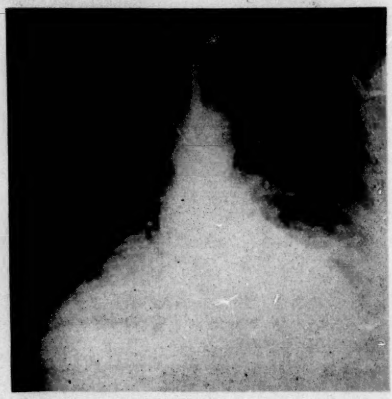

FIGURE 4. *Tumor Mass at the Right Hilus in Case 9, Producing Partial Atelectasis of the Right Lower Lobe.*

lipiodol studies are to determine the site of a suspected tumor when bronchoscopy fails to do this, and to ascertain the presence of bronchiectasis. When the latter is being sought, it may be necessary to remove a portion of the adenoma prior to bronchography to obtain satisfactory filling. In Case 1 bronchograms showed obstruction of the dorsal division of the right-lower-lobe bronchus. In Case 5 bronchiectasis was demonstrated, but the tumor mass, which was largely extrabronchial, was not apparent.

DIAGNOSIS

Bronchial adenoma should be considered as a diagnostic possibility in every young patient who presents a history of chronic cough, hemoptysis and repeated pulmonary infections. Likewise, the possibility of adenoma should be entertained in the presence of atelectasis, localized wheeze, obstructive emphysema or unilateral bronchiectasis. The prime requisite to the diagnosis is to suspect bronchial adenoma and to obtain bronchoscopy. Visualization of the tumor and microscopical study of biopsy material usually establish the diagnosis. The main points of differentiation from bronchiogenic carcinoma have been discussed. Bacteriologic studies of bronchial secretions are important in ruling out tuberculosis; however, the two conditions can coexist. An intrabronchial foreign body can be distinguished in most cases by the history of aspiration.

TREATMENT

Therapy of bronchial adenoma has been almost entirely confined to local removal and to surgical resection. Irradiation has been given a limited trial but has proved of questionable value. This form of treatment was employed in Case 2 with temporary decrease in cough and hemoptysis, but without

FIGURE 5. *Obstructive Emphysema of the Right Lung in Case 3, Produced by the Valve-like Action of a Pedunculated Bronchial Adenoma.*

Note the low position of the right leaf of the diaphragm and shift of the heart to the left.

visible change in the tumor itself, which was later removed by electrocoagulation.

Bronchoscopic removal affords good results in selected cases, specifically those in which the adenoma has a distinct pedicle and no extrabronchial extension, and in which irreversible pulmonary damage has not occurred. Local removal is the only possible approach to adenomas that involve the

carina. It may be employed to promote bronchial drainage prior to surgical resection, thereby reducing the degree of infection.

Surgical resection holds the advantage of removing not only the entire tumor but also the infected portion of the lung. Bronchiectasis in itself is an indication for resection, regardless of whether or not the tumor can be completely removed bronchoscopically. In addition, surgical resection precludes the possibility of malignant degeneration, which, although relatively infrequent, cannot be entirely discounted. It might be argued that resection is too radical for sessile adenomas without demonstrable extrabronchial tumor or infection, and yet the probability of later complications after local removal is sufficiently great to make lobectomy or pneumonectomy the preferred method of treatment.

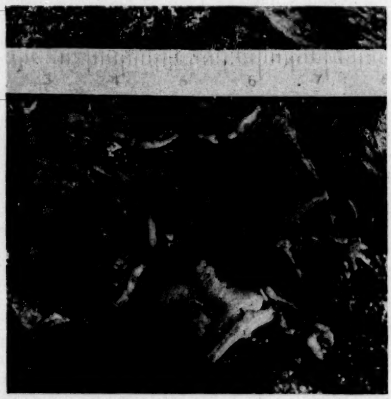

FIGURE 6. *Surgical Specimen in Case 15, Showing a Small Adenoma in situ at the Bifurcation of the Left Main Bronchus. The tumor mass arose in the main bronchus, extended into the upper-lobe bronchus and almost completely occluded the lower-lobe bronchus. A portion of the adenoma had previously been removed for biopsy.*

This is especially true today with the great reduction in mortality and morbidity that has resulted from improved surgical technic and from the use of antibiotics.

In 3 patients of the present series the adenomas were removed bronchoscopically without a recurrence to date. Case 2 was treated by local removal prior to the evolution of the present policies of treatment; there has been no recurrence after six and a half years. The adenoma in Case 3 had a distinct pedicle, which rendered bronchoscopic removal practicable; this patient has remained well for four and a half years. In Case 10 the tumor arose in the right main bronchus and encroached upon the carina; electrocoagulation was carried out without recurrence after seven months. Another patient (Case 1) was bronchoscoped seven times over a six-year period; although the endobronchial portion of the tumor was successfully obliterated, extrabronchial growth produced progressive broncho-

FIGURE 7. *Bronchial Adenoma in Case 15, Showing Intraluminal Growth and Infiltration of the Bronchial Wall, with Replacement of the Normal Glandular Structure (x 11½).*

stenosis, bronchiectasis developed, and lobectomy became necessary. In Case 12 the tumor involved both the left-upper-lobe and the left-lower-lobe bronchi; therefore, it was decided that trial by local removal was justified in an attempt to avert pneumonectomy. The growth recurred within two months, and pneumonectomy was performed without further delay. In Case 15 the tumor was located at the bifurcation of the left-upper-lobe and left-lower-lobe bronchi (Fig. 6); pneumonectomy was done without trial of local removal. Infiltration of the bronchial wall by tumor cells is shown in Figure 7.

The left lung was removed in 3 cases. Two lobes were resected in 5 patients, and a single lobe in 3. The remaining patient underwent pneumonectomy elsewhere and has been lost to follow-up observation. There were no operative deaths. Five months after removal of the left lung the patient in Case 12 developed difficulty in swallowing; barium studies revealed distortion of the esophagus by the bronchial stump, without obstruction. The other 10 patients have been completely relieved of their symptoms and have remained well for from six months to six and a half years postoperatively, except 1 (Case 15), who was operated on too recently to be included in the follow-up report.

SUMMARY AND CONCLUSIONS

Bronchial adenoma constituted 6.9 per cent of all pathologically proved primary bronchial tumors

encountered at the Lahey Clinic over a period of eighteen years. Adenomas can usually be visualized bronchoscopically, and their characteristic appearance in most cases serves to differentiate them from carcinoma. Bronchial adenoma is a potentially malignant tumor, but the malignancy is of a low grade.

Sixty per cent of bronchial adenomas occurred in patients less than forty years of age. The incidence was slightly greater in female patients. A history of chronic cough, hemoptysis and repeated pulmonary infections, or findings of atelectasis, localized wheeze, obstructive emphysema or unilateral bronchiectasis are indications for bronchoscopy on a suspicion of adenoma.

Inasmuch as surgical resection removes the infected lung tissue as well as the entire tumor and prevents malignant degeneration, it is the treatment of choice in the majority of cases. Local removal may suffice for pedunculated adenomas without extrabronchial extension and without irreparable parenchymal destruction; however, the possibility of recurrence necessitates repeated bronchoscopic examinations.

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PSYCHIATRY IN A GENERAL HOSPITAL OF A SMALL CITY*

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PSYCHIATRY is slowly becoming part of general-hospital organization. This branch of medicine was preceded by neurology, which is concerned with more obvious physical disease and usually does not involve overt abnormalities of behavior. The patient with a psychiatric diagnosis is not welcome in a general hospital. His diagnosis meets the resistance of outmoded attitudes. His illness is still not devoid of some social stigma. Hospital personnel are too apt to associate memories of excitements and unco-operative behavior with psychiatric disorders. To circumvent such conditions, psychiatric patients are admitted daily to general hospitals with nonpsychiatric diagnoses. Bennett[1] reports that in 1940 there were 4302 general hospitals in the United States, more than 90 per cent of which did not permit the admission of a patient with a known psychiatric diagnosis.

In spite of such resistant attitude toward psychiatric patients, some definite progress has been made. Many hospitals offer psychiatric consultation. However, only hospitals with locked pavilions offer any active or complete treatment. Such locked pavilions are few in number and are usually limited to large hospitals or those associated with teaching institutions. Heldt's[2, 3] reports on the psychiatric division of the Henry Ford Hospital were notable and early exceptions. It is of interest that at the Henry Ford Hospital, psychotic patients were admitted even though locked facilities were not available. However, a full-time psychiatric staff cared for these patients.

With the advent of shock therapies, new opportunities for treatment of psychiatric disorders have been offered to the average general hospital. Selected patients, even though suffering from major disorders, can fit into the hospital setting for a reasonable period. Fetterman[4] has emphasized the value and feasibility of treating psychiatric patients in a general hospital. During a recent visit to the Royal Victoria Hospital in Montreal, I was able to view an entire building, the Alan Memorial, devoted to the treatment of neurosis and psychosis without the aid of locked wards. In the Army, small hospitals often had to care for psychotic patients. In civilian medicine the smaller general hospitals have made practically no attempt to care for the psychiatric patient. My experiences in developing a practical degree of psychiatric service in a general hospital of a small city are reported below.

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It is believed that these experiences may be of value to others who wish to develop similar facilities.

In May, 1946, a tentative plan for the treatment of selected psychiatric patients in the House of Mercy Hospital, Pittsfield, Massachusetts, was embarked on. The plan was formulated with the co-operation of the hospital medical director, Dr. Reo J. Marcotte, who recognized the responsibility the hospital would assume, but also recognized the service that could be performed for the benefit of the community. The House of Mercy Hospital is a general hospital of 200-bed capacity. It is the largest of three in the City of Pittsfield, which has a population of about 55,000. There is also an additional population of 75,000 in the county. The neuropsychiatric program was started without any significant expense to the hospital. In the Outpatient Department, several rooms that had not previously been fully utilized were designated as the "treatment area." The nurses assigned to the Outpatient Department plan their schedule so that they are available for treatments, which are given at approximately the same time each morning. A male attendant is also available at such treatment periods. Personnel of this type are especially necessary when electric convulsive therapy is administered. In the treatment area, subcoma insulin and sodium amytal interviews are also carried out. Subcoma insulin treatments are supervised by the same nurses. Patients are treated on an inpatient or outpatient basis. Inpatients who have improved are often discharged, and treatment is continued on an outpatient basis.

This psychiatric program is carried on without assistance from hospital interns or residents. Although it would be desirable to have such doctors participate in the program, there has been a marked shortage of house officers in the smaller general hospitals. Medical supervision of the program depends entirely on myself, the only physician taking part in the program. I spend all my mornings in the hospital, and in this way all treatments can be properly supervised.

The success of the plan for the management of psychiatric patients depends largely on selection. Since there are no locked facilities, a significant number of patients must be rejected. It is apparent that disturbed, overactive, unco-operative and some paranoid patients cannot be accepted for treatment. In the psychotic group of patients, depressions comprise the largest number. Psychotic patients are accepted for treatment when it appears that they can be helped by electric shock therapy. Psychoneurotic patients are accepted when psychotherapy in a hospital setting is considered advantageous, and when it is believed that somatic treatment will be of value. The largest number of these patients have severe anxiety tension states and have been difficult to manage on the basis of office treatment. Such patients are treated with psychotherapy and subcoma insulin. Patients with conversion states are hospitalized and are treated with psychotherapy, aided by sodium amytal interviews.

Table 1 presents a report of the patients treated during the year 1947. It is realized that the numbers are not impressive. However, the figures should be considered in relation to the size of the community. No attempt is made to evaluate the somatic treatments used, since these have been adequately discussed elsewhere.

It can be seen that a higher percentage of psychotic patients were treated as outpatients. This was often due to the patient's inability to co-operate in a general hospital. It would probably have been better to institutionalize several of these patients. However, neither the patient nor the family was able to make such a decision. To refuse treatment to such patients would have meant that they would merely remain at home.

TABLE 1. *Inpatients and Outpatients Treated during 1947.*

DIAGNOSIS	NO. OF CASES	
Inpatients:		
Psychoneurosis	42	
Psychosis	14	
		56
Outpatients:		
Psychoneurosis	8	
Psychosis	20	
		28
Total		84

The management of psychiatric patients in a general hospital, without locked facilities, has significant advantages. Patients are treated without legal commitment or certification. At an early date the family and patient can more readily accept the psychiatric diagnosis and the indicated treatment. Relatives are reassured when they realize that the patient is to be treated in the same hospital where he would receive care for pneumonia or appendicitis. This minimizes any question of social stigma. In this community it means that the patient does not have to be removed to some other city, since there are no other psychiatric hospital facilities in Pittsfield. Patients who are treated on an outpatient basis spend only short periods away from their home setting.

These advantages not only are important in their social implications but also include significant economic elements. Since the patient remains in the community, time and money are not spent in traveling to visit him. Hospitalization insurance has recently been liberalized and gives definite benefits to the psychiatric patient. In this community a large industrial organization has liberalized its hospitalization policy and allows both inpatient and outpatient treatment of psychiatric patients. Blue Shield in Massachusetts makes extra allowances to the physician for the

administration of shock therapy. In all, these changes have brought the economics of a psychiatric disorder close to that of other medical and surgical diseases.

It is recognized that this plan has definite disadvantages. Suicidal attempts are always a potential danger. Fortunately, there have been no such accidents in the hospital. However, there have been three unsuccessful suicidal attempts in patients receiving electric shock therapy on an outpatient basis. It can be seen that the plan often places an unusual responsibility on the family. Inpatients do not have the advantage of a planned occupational-therapy program.

Summary and Conclusions

The general hospital of the smaller cities can offer treatment for psychiatric patients.

A description is given of the development of the program for treatment of psychoneurosis and psychoses in the House of Mercy Hospital, Pittsfield, Massachusetts.

A program for psychiatric treatment can be carried out under the supervision of one psychiatrist.

The success of the program is largely dependent on the selection of patients.

Treatment of the psychiatric patient in a general hospital has significant medical, social and economic advantages.

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CLINICAL NOTE

GIANT OVARIAN CYST IN A NEWBORN INFANT*

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and
Henry W. Hudson, Jr., M.D.‡

OVARIAN cysts producing symptoms in early life are rare, and in the newborn infant almost unknown. Symptoms are almost invariably the result of torsion. Diagnosis is seldom made prior to operation. Doran,[1] in 1888, described the postmortem appearance of a seven-month premature infant who survived birth by a few minutes as follows:

> The abdomen was distended, the subcutaneous veins were prominent. The integuments above the level of the umbilicus were discolored through ecchymosis.

In 1936 Haines and Edgerly[2] made a review and reported cases of cysts being removed for abdominal symptoms but not for symptoms suggesting intestinal obstruction. A similar review was presented by Benjamin[3] in 1941.

In 1942 Bulfamonte[4] described a case quite similar to that reported below.

Case Report

A female infant was born, at term, on April 22, 1947, at 8:15 a.m. The mother had been greatly impressed by the large amount of amniotic fluid when the membranes ruptured spontaneously 2 hours before birth. She estimated the amount as several times greater than that with any of her previous seven pregnancies.§ No abnormality of the infant was noted by the two physicians present at delivery nor by a physician who saw the baby at 10 a.m. because of cyanosis relieved by aspiration of mucus. The infant went to breast 12 hours after delivery and every 4 hours thereafter, and the mother noted that little or nothing was taken and that the infant was continuously spitting "saliva," which at the end of the first 24 hours of life was yellow stained.

On April 23 at 8 a.m. physical examination revealed the abdomen to be markedly distended, and several engorged veins were noted over the upper part. The percussion note was tympanitic over the upper abdomen and dull in the flanks and over the lower abdomen. Peristaltic sounds were audible only in the right upper quadrant and faintly in the right flank. No mass was made out, but a sense of increased resistance was observed in the left lower quadrant. No fluid wave was demonstrated. The examiner was unable to introduce his little finger into the anus. No meconium had been passed.

Examination of the blood was not significant except that the white-cell count was 19,100. X-ray examination was reported as showing moderate distention of the stomach and numerous loops of small bowel and parts of the large bowel. These gas-filled loops lay primarily in the right upper quadrant and the right posterior gutter. The left anterior portion of the abdomen was occupied by a fairly homogeneous shadow without any evidence of identifying characteristics. The descending colon and sigmoid contained a small amount of gas. An attempt to outline the large bowel by injection of lipiodol showed only the distal 10 cm. The oil could not be introduced beyond this point, presumably because of a considerable amount of meconium rather than an organic lesion. The general impression was one of almost complete intestinal obstruction, probably resulting from an intrinsic lesion or anomaly of development. Distention increased rapidly, and by 4:30 p.m. was extreme. Cyanosis was noted. The superficial veins of the abdominal wall were greatly dilated. About 1 cm. below the xiphoid a line of demarcation was apparent, below which the skin was dusky; the legs were definitely cyanotic. Venous obstruction and intestinal obstruction seemed evident. A catheter was passed into the stomach, but little or no air obtained. Operation was performed 34 hours after birth. Various diagnoses, all concerned with possible causes of intestinal obstruction, were entertained.

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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§The possible association of hydramnios and anomalies of the intestinal tract in the fetus is recognized by various authorities.

The peritoneal cavity was explored through a transverse incision and a tense cystic mass (Fig. 1) exposed. This proved to be a thin-walled, unilocular cyst measuring more than 12 by 10 by 5 cm. and under tension. Its attachment was immediately proximal to the fimbriated end of the left fallopian tube. There was a little gas and meconium in the large bowel, the small bowel being collapsed and compressed by the mass of the cyst. The cyst was removed intact, and its color changed from a light blue, before removal, to a pinkish yellow after removal. The intestinal tract from stomach to rectosigmoid was examined and considered normal. The wound was closed.

Review of the anesthesia chart revealed an immediate improvement in pulse, color and amplitude of respiration after delivery and removal of the cyst.

The patient's weight at birth was 6 pounds, 6 ounces. Immediately after operation it was 6 pounds, including the dressing. Convalescence was delayed by low serum protein with edema, which was corrected, and she was discharged

FIGURE 1.

34 days after operation, weighing 7 pounds, 4 ounces. In October, 1947, she was considered to be in good condition and developing normally.

The specimen was immediately photographed. It was then covered with gauze, soaked in physiologic saline solution and placed in a container with ice. The specimen was taken to the Fearing Research Laboratory, Free Hospital for Women, Brookline, Massachusetts, where Drs. O. Watkins Smith and George V. Smith were consulted about a possible assay of the cyst fluid. The intact cyst weighed 340 gm. It was aspirated, and approximately 300 cc. of fluid removed for assay. The removed fluid was partially replaced by a solution of formalin, and the needle puncture area was ligated. The specimen was examined in the Department of Pathology, Children's Hospital, Boston. The microscopical slides were reviewed by Drs. George V. Smith and Arthur T. Hertig, who concurred in the microscopical diagnosis made by the Children's Hospital Laboratory.

The pathological report was as follows:

The specimen consists of a roughly spherical, fluctuant, translucent, formalin-fixed mass weighing 340.7 gm., and measuring 12 by 10 by 5 cm. The external surface is smooth and glistening and is mottled purple red in color. Through the wall are seen numerous fine vascular markings. Along one edge there is a tubular structure measuring 2.5 by 3.0 cm. One edge is closed by a silk suture, and the other resembles the fimbriated end of a fallopian tube. There is also noted a nipple of tissue surrounded by a silk suture. On section there is revealed an estimated 150 cc. of clear yellow fluid with the odor of formalin. The inner lining is smooth and glistening with prominent blood-vessel markings, and there are several small cystic nodules opposite the cylindrical structure on the external surface described above. They measure 0.2 to 0.5 cm. in diameter and contain a clear yellow fluid. The wall is of uniform thickness throughout.

Microscopical examination revealed two sections stained by hemotoxylin and eosin and two Giemsa-stained sections,

FIGURE 2.

which include the fallopian tube and a segment of the cyst wall. The mucosa of the fallopian tube is drawn into its usual folds. The muscularis is moderately cellular and somewhat edematous. The cyst wall is largely composed of fine strands of connective tissue, which are loosely interwoven. The lining of the cyst is composed of from three to eight layers of flattened cells with elongated nuclei resembling fibroblasts, with a moderate number of cells with round, tense nuclei resembling granulosal cells. Nowhere in the section is there any evidence of inflammation or neoplasm (Fig. 2).

The diagnosis was follicular cyst of ovary and fallopian tube.

The estrogenic assays made in the Fearing Reasearch Laboratory gave the following result: the cyst fluid was found to contain 5.0 international units of estrogenic activity per cubic centimeter. No ketonic estrogen was demonstrable; 80 per cent of the total activity went into the estradiol fraction. This division of estrogenic material is similar to that found in follicular cysts of the ovary in older persons, which, however, contain more estrogenic activity (25 to 450 international units per cubic centimeter).

SUMMARY

The case of a thirty-four-hour-old infant from whom a gigantic follicular cyst of the ovary was successfully removed is presented.

A report of the histologic examination and assay of contents of the cyst is made.

A review of the literature reveals only 1 case of successful operation in a newborn infant for a similar lesion.

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MEDICAL PROGRESS

METHEMOGLOBINEMIA AND SULFHEMOGLOBINEMIA*

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BOSTON

THE appearance of severe cyanosis may alarm the patient and presents a diagnostic problem to the attending physician. Recognition of the cause of the cyanosis and the specific blood pigment involved permits the separation of conditions connoting serious underlying disease from those of benign origin. An increased amount of reduced hemoglobin in cardiac or pulmonary disease is frequently responsible for mild cyanosis. The more intense degrees of cyanosis seen clinically are due to abnormal pigments within the red cell — methemoglobin and sulfhemoglobin. The relative capacity of each of these pigments to produce cyanosis is shown by the fact that about 5 gm. of reduced hemoglobin per 100 cc. of blood is required to produce recognizable cyanosis,[1] whereas 1.5 gm. of methemoglobin and less than 0.5 gm. of sulfhemoglobin have comparable effects. Rarely, cyanosis is produced by intravascular hemolysis with the formation of methemoglobin and methemalbumin[2] in the plasma. In such cases, the associated anemia, hemoglobinuria and side effects of the toxic agent are conspicuous, and the cyanosis is relatively mild. The presence of hemoglobin and its derivatives in the plasma differentiates this group from intracellular cyanosis, although combined reactions may occur. This discussion is limited to abnormal pigments within the red cell that produce cyanosis.

INTRACELLULAR METHEMOGLOBIN

Hemoglobin iron is normally ferrous, and in its role as an oxygen carrier is oxygenated and de-oxygenated without change in valence. In methemoglobin the iron has been oxidized from the ferrous to the ferric form.[3] The change is an easily reversible one and in itself is not accompanied by any red-cell damage or destruction.[4–7] Methemoglobin is unable to transport oxygen and should therefore be regarded as a pigment that is temporarily inert.

Identification

When methemoglobinemia is suspected, blood should first be drawn into a tube containing heparin or oxalate and centrifuged. If the plasma is clear, hemolysis and abnormal serum pigments are excluded as a cause of cyanosis. The whole blood may then be shaken in air for fifteen minutes. Normally, the blood becomes bright red as all pigment is converted to oxyhemoglobin. If it remains dark, abnormal intracellular pigments are present. The blood should then be diluted ten to one hundred times with water and examined with a hand spectroscope. The dark band of methemoglobin is seen at 630 millimicrons (Fig. 1). The band disappears immediately after two or three drops of 5 per cent potassium cyanide are added, differentiating it from the sulfhemoglobin band at 618, which remains fixed.[8, 9] The same bands may be seen through the earlobe of the patient. Methemoglobin may be determined quantitatively by gasometric means[10] or colorimetrically.[11] Horecker[12, 13] has described its absorption spectrum in the infrared and devised a method for its measurement in this range. In all quantitative determinations in the visible range, the importance of controlling the pH is shown by the spectrophotometric studies of Austin and Drabkin.[14] Blood should be examined within one or two hours of withdrawal since in most cases intracellular methemoglobin on standing spontaneously reverts to the ferrous form.[15]

Hemoglobin-Methemoglobin Equilibrium of the Erythrocyte

The relation between hemoglobin and methemoglobin is more clearly understood by a comparison of its equilibrium in three systems — that is, in water, in plasma and within the erythrocyte (Fig. 2). Under aerobic conditions an aqueous hemoglobin solution is progressively converted to methemoglobin. In plasma, free hemoglobin is only partially converted to methemoglobin.[16, 17] By means of certain reducing substances the plasma appears to be able to maintain the equilibrium at somewhat over 50 per cent ferrous hemoglobin. In contrast, the normal erythrocyte contains at most only 1 or 2 per cent of methemoglobin.[10, 18–20] The question then arises regarding how hemoglobin within the erythrocyte is maintained in the ferrous form.

Although devoid of a nucleus, the red cell energetically reduces methemoglobin by an enzymatic process in which glucose and lactate are the principal substrates.[21–28] The presence of methemoglobin activitates this process since the resting oxygen consumption and glucose utilization of the red cell are only slight, whereas in the presence of methemoglobin there is an appreciable

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increase. Methemoglobin offers an available source of oxygen for carbohydrate breakdown and in the process is itself reduced. It appears that hexose monophosphate, reduced pyridine nucleotide and perhaps Kiese's "methemoglobin reductase" are involved in this reduction. Since with lysis of the red cell the phosphorylating mechanism breaks down and pyridine nucleotide is destroyed, the system can operate only in the intact cell. Clinical states of methemoglobinemia can be caused either by *dysfunction of this reconversion mechanism*, without which circulating hemoglobin would be at the mercy of the plasma oxidation-reduction potential, or by the *action of oxidants*, which produce methemoglobin more rapidly than the cell mechanism is able to reduce it (Fig. 2). With the existing equilibrium between oxidized and reduced hemoglobin within the erythrocyte, it would be anticipated that much larger amounts of oxidants would be needed to produce successive increments of methemoglobin. Indeed, in animals it is almost impossible to displace this equilibrium to the lethal point with certain aniline derivatives.[29–31]

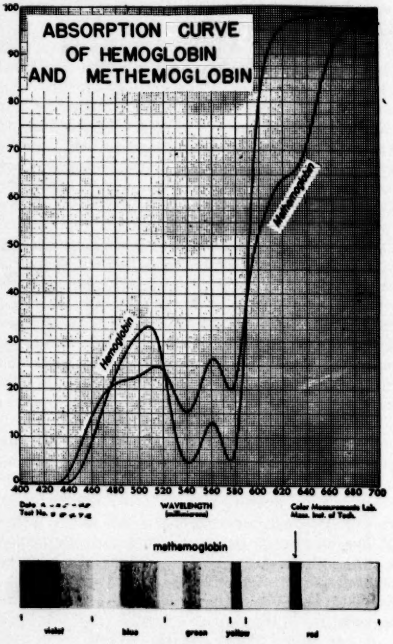

FIGURE 1. *Spectrophotometric Absorption of Methemoglobin. In the upper portion the percentage transmission of a solution of oxyhemoglobin is compared with a solution of both methemoglobin and oxyhemoglobin. The decreased transmission (or increased light absorption) of the methemoglobin solution at 500 and 630 millimicrons is evident. Below is a spectrum as visualized through a hand spectroscope (adjusted to the wavelength-scale above) in which the typical band of methemoglobin in the red is shown by an arrow.*

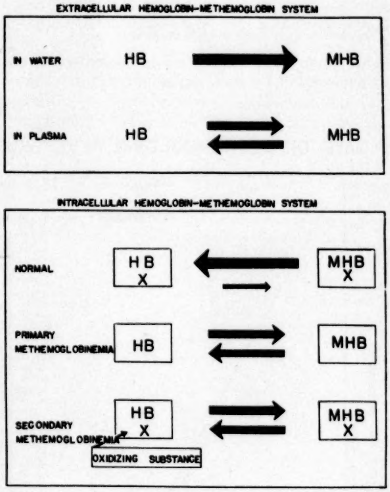

FIGURE 2. *Hemoglobin (HB) and Methemoglobin (MHB) Equilibriums.*

X represents the normal-functioning methemoglobin reconversion system of the erythrocyte. The arrows designate the nature of the equilibriums under different conditions. Blood hemolyzed in water is progressively and completely converted to methemoglobin. It is apparent that in respect to the hemoglobin-methemoglobin equilibrium, the red cell in congenital methemoglobinemia is similar to hemoglobin suspended in plasma. In both, methemoglobin is found in amounts slightly below 50 per cent. Although the red-cell mechanism (X) maintains a ratio of about 99 HB:1 MHB, oxidizing substances may temporarily displace this equilibrium.

Physiologic Effects of Methemoglobinemia

Symptoms from methemoglobinemia are attributable to the anoxia produced by the lowered oxygen capacity of the blood or to side effects of the agent producing methemoglobinemia. At concentrations of 20 per cent methemoglobin, working subjects complained of mild fatigue and showed abnormally high blood lactic acid levels.[32] In dogs with methemoglobin concentrations over 40 per cent, a compensatory increase in cardiac output has been observed.[33] A shift in the oxygen dissociation curve to the left has been shown to occur in

drug-induced methemoglobinemia, seriously handicapping the unloading of oxygen in the tissues.[34, 35] Despite this, levels of 30 to 50 per cent methemoglobin may occur without producing severe symptoms.[5] The lethal concentration of methemoglobin in dogs is about 85 to 90 per cent.[36] The exact level at which coma and death supervene in man is not known.

Treatment of Methemoglobinemia

Methemoglobin in the body may be reconverted to hemoglobin by reducing substances, by the normal cell-reconversion mechanism or by catalysis of this normal mechanism.

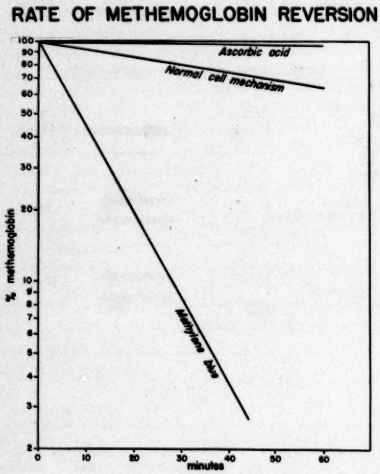

FIGURE 3. *Various Reversion Rates Calculated from Data Presented Elsewhere.*[39]

The ordinant represents the percentage of the initial level of methemoglobin, usually between 2 and 5 gm. per 100 cc. in the patients studied.

Ascorbic acid[37] and glutathione[38] are effective as reducing agents, although the only one used clinically has been ascorbic acid. This substance reduces methemoglobin slowly in vivo and even in large doses does not approach the speed of the normal cell-reconversion system.[39] This material is of little value, therefore, in conditions in which the normal cell-reconversion mechanism may have been exceeded — that is, in secondary methemoglobinemia (Fig. 3).

Methylene blue brings about reversion of methemoglobin not by its own reduction capacity but through acceleration of the normal cell-reconversion mechanism. Perhaps the first suggestion of its role in red-cell metabolism was the observation of Harrop and Barron[40] that red-cell respiration and carbohydrate utilization are increased greatly by methylene blue. In tissue respiration methylene blue is able to substitute for the cytochrome enzymes. Mammalian red cells lack these enzymes. Since the dye accelerates red-cell respiration and methemoglobin reduction to a state comparable to that found in nucleated avian erythrocytes, it may be postulated that it acts as a more efficient oxidation-reduction transport system than that present in the mammalian erythrocyte. Methylene blue reverts methemoglobin at a rate far greater than that of the normal cell mechanism, as shown in Figure 3.[39, 41–43]

The misleading statement is sometimes made that methylene blue may either reduce methemoglobin or produce it depending on the dose employed. However, over a dosage range of a fraction of a milligram to 10 mg. per kilogram of patient's body weight, methylene blue acts to revert methemoglobin to hemoglobin and *clinically significant amounts of methemoglobin are not produced.*[44–46] Doses of 500 mg. administered intravenously during ten minutes in man have produced symptoms of nausea, precordial and abdominal pain, dizziness and headache, and mental confusion for as long as twelve hours.[47] Larger doses up to 7 gm. administered slowly have been given without symptoms but have produced anemia in man.[46] Still larger doses in animals have produced hemolytic anemia, pulmonary edema and death.[48, 49] In the usual therapeutic dose of 1 or 2 mg. per kilogram of body weight, given over a five-minute period, however, no such reactions have been reported.

Specific treatment for methemoglobinemia has been discussed elsewhere.[39] After the pigment has been identified, 1 mg. of methylene blue per kilogram of body weight in adults and 2 mg. in infants may be injected intravenously slowly over a period of five minutes.* If cyanosis has not disappeared within an hour, a second dose of 2 mg. per kilogram of body weight should be given. Methylene blue may also be given orally in doses of 3 to 5 mg. per kilogram.

CLINICAL METHEMOGLOBINEMIA

Primary Methemoglobinemia

In the literature at least 16 established cases of congenital methemoglobinemia have been reported,[50–61] in 8 of which there was a familial incidence. In 5 other cases information regarding the congenital aspect was incomplete.[62–65] Symptoms consisting of fatigue, exertional headaches and reduced exercise tolerance are surprisingly mild. I have seen 1 patient with a methemoglobin level of 40 per cent who was able to indulge in strenuous

*For intravenous injection 1 per cent solutions are prepared by Parke, Davis and Co. and by William H. Rover, Incorporated. The usual adult dose is 7 cc.

activity without symptoms. This remarkable tolerance to methemoglobinemia may be explained by its chronicity, by the secondary polycythemia compensating for inert pigment and by the normal oxygen-dissociation curve in contrast to secondary methemoglobinemia.[5] Reports indicate that without treatment the majority of these patients tend to reach equilibrium at about 40 per cent methemoglobinemia.

In blood drawn from these patients, methemoglobin shows no tendency to revert to hemoglobin spontaneously. The biochemical lesion, a failure of the normal reconversion mechanism, represents a congenital defect of the erythrocyte. Methemoglobin accumulates slowly until a point of equilibrium is reached. In 1 patient studied it was produced at the rate of 3 per cent of the total pigment a day.[5] The ascorbic acid of the serum is decreased in these patients despite adequate diets,[56, 59–61] and the plasma has little or no capacity to reduce methemoglobin.[60] This suggests that reducing substances are being expended in the reduction of methemoglobin to hemoglobin. These reducing substances may be regarded as a secondary line of defense of the body against pigment oxidation. Patients may be adequately treated with either ascorbic acid or methylene blue. Lian[55] first described the efficacy of ascorbic acid in congenital methemoglobinemia, and this has been verified by others.[5, 56, 59–61] In doses of 100 to 500 mg. a day by mouth, the methemoglobin levels are reduced to 8 to 10 per cent of the total pigment. This might be anticipated since the rate of reconversion by ascorbic acid is considerably greater than the spontaneous methemoglobin accumulation in these patients.[39] Methylene blue is likewise effective in a daily dosage of 100 to 300 mg. by mouth.[5]

Secondary Methemoglobinemia

That due to drugs. Certain drugs or their degradation products have the capacity of converting hemoglobin to methemoglobin. These drugs preferentially oxidize hemoglobin, and reducing substances in the body such as glutathione and ascorbic acid offer no protection against this oxidation.[66] Some of these drugs are listed in Table 1. It seems probable that the amino and nitro groups of these compounds are responsible for the methemoglobinemia. Nitrites, sulfonamides and aniline derivatives are perhaps the most important drugs in the production of methemoglobinemia.

Nitrites produce methemoglobin rapidly and quantitatively within limits when studied in vitro or in vivo, although the exact chemical interaction is not clear.[78] The many ways in which nitrites gain access to the blood stream have presented numerous clinical problems. Cyanosis may be produced by excessive use of amyl nitrite or nitroglycerin, or by inhalation of nitrous gases as reported in arc welders.[79] Ingested nitrates may be converted to nitrites by intestinal bacteria, and, after absorption from the intestine, produce methemoglobin. Cases have been reported in infants drinking well water that had high concentration of nitrates,[80–82] from the use of bismuth subnitrates in the treatment of diarrhea,[83, 84] from ammonium nitrate used as a diuretic[85] and from food high in nitrates.[86] Methemoglobin is especially prone to occur after nitrate ingestion in patients with ulcerative lesions of the bowel.

Sulfonamides — particularly sulfanilamide, but also prontosil, sulfathiazole and sulfapyridine — frequently produce both methemoglobin and sulfhemoglobin.[87–94] No report has been found of this type of cyanosis due to sulfadiazine or sulfamerazine. Rimington and Hemmings[95] have attempted to correlate the porphyrinuric action of these drugs with their methemoglobin production capacity.

TABLE 1. *Amino and Nitro Compounds Producing Methemoglobinemia.**

Aromatic Drugs	Aliphatic and Inorganic Drugs
Aniline	Sodium nitrite
Anilinoethanol	Hydroxylamine
Phenacetin	Dimethylamine
Acetanilid	Nitroglycerin
Methylacetanilide	Amyl nitrite
Hydroxylacetanilide	Ethyl nitrite
Prontosil	Bismuth subnitrate
Sulfanilamide	Ammonium nitrate
Sulfapyridine	
Sulfathiazole	
Phenylenediamine	
Aminophenol	
Toluenediamine	
Alphanaphylamine	
Paraminopropiophenone	
Phenylhydroxylamine	
Tolylhydroxylamine	
Nitrobenzene	
Dinitrobenzene	
Trinitrotoluene	
Nitrosobenzene	
Paranitraniline	

*Based on various reports in the literature.[34, 47–77]

Aniline dyes are particularly dangerous because of their ability to penetrate the intact skin,[96–99] producing methemoglobinemia through the action of breakdown products — that is, phenylhydroxylamine and aminophenol. Contact with dyed blankets, laundry marks on diapers and freshly dyed shoes has produced methemoglobinemia. A single washing of the dyed article will prevent this. Recently, several cases of methemoglobinemia have been observed in children swallowing colored crayons.[100] Owing to their extensive use, phenacetin and acetanilid are two of the more common drugs producing methemoglobinemia.[101]

Associated red-cell damage varies considerably from one drug to another and even with the same drug from one patient to another. The over-all picture is best represented as a spectrum with methemoglobin formation at one end and extensive red-cell destruction at the other. Nitrites cause chiefly methemoglobinemia, although Heinz bodies and anemia have been described in chronic poison-

ing. Phenylhydrazine, on the other hand, acts in vivo to produce only red-cell destruction. Some drugs, — for example, the sulfonamides, — which produce predominantly methemoglobinemia, on some occasions cause extensive cell destruction.[102, 103] Drugs such as potassium chlorate and arsine[104] produce massive hemolysis but also methemoglobinemia. It appears that methemoglobin formation secondary to drugs may be regarded as a mild and reversible form of cell injury and that more severe cell damage frequently occurs and should always be looked for.

The rapidity of methemoglobin production of these various drugs is dependent upon their metabolism within the body and on their excretion. Although the effect of intravenous nitrite is expended within an hour, nitrobenzene does not produce its maximum effect for twelve to fifteen hours.[105] The duration of action of the drug is of importance in anticipating the duration of the methemoglobinemia produced. As pointed out above, the reversion mechanism of the erythrocyte will, within a few hours, convert methemoglobin back to hemoglobin unless there is some oxidant acting in the opposing direction.

In drug-induced methemoglobinemia, the capacity of the normal red-cell reconversion mechanism may be assumed to have been exceeded, and substances that act less rapidly than this normal mechanism, as ascorbic acid does, have no place in its therapy (Fig. 3).[39, 43] On the other hand, methylene blue is extremely effective as evidenced by numerous reports in the literature.[42, 43, 91, 106] Should the cyanosis not respond to methylene blue, one must suspect either that a large quantity of oxidizing substance is present, which is still able to displace the equilibrium despite the action of methylene blue, or that some other pigment, such as sulfhemoglobin, is present. It has been suggested, on the basis of observations in vitro, that in some cases methemoglobin may be produced indirectly by drugs through the destruction of erythrocyte catalase, thus rendering the erythrocyte vulnerable to oxidation.[107] This awaits clinical verification.

Enterogenous Methemoglobinemia

Since the reports of Stokvis[108] and Talma[109] in 1902, the term enterogenous cyanosis has appeared repeatedly in the literature. Some justification for the acceptance of this as a clinical syndrome is the similarity of the case reports.[110–114] The patients usually have abdominal pain with diarrhea, or constipation. There are attacks of slate-blue cyanosis accompanied by headache, often shortness of breath, dizziness, collapse and syncope; van den Bergh[111] demonstrated nitrite-producing bacteria in the stools and nitrites in the blood of such patients. It was postulated that because of the gastrointestinal disease, there was an abnormal production and absorption of nitrites. As pointed out by van Lier,[82] however, many of these patients were taking aniline derivatives for headache, and, at the time of these early reports, the capacity of these drugs to produce methemoglobinemia was not appreciated. Certainly, some of the cases may have been due to drugs, the intestinal lesions being contributory but not causative.[82, 115–117] In contrast to primary methemoglobinemia, anemia is frequently present in this group, and indicanuria is found. Van den Bergh noted an increase in cyanosis shortly after meals and suggested a milk diet and enemas, which resulted in improvement in several cases. Under the heading of enterogenous cyanosis, cases have been reported of both methemoglobinemia and sulfhemoglobinemia, often not distinguished spectroscopically in the reports. It seems likely that the two occur together more often than reports indicate.[112, 114] For convenience, enterogenous methemoglobinemia and enterogenous sulfhemoglobinemia are discussed separately in this paper. It will be apparent, however, that their separation is artificial. It is not difficult to distinguish the two pigments in detailed case reports, since methemoglobin is quickly reverted to normal and therefore shows a rapidly changing blood level, whereas sulfhemoglobin gradually disappears from the circulating blood over a period of two or three months.

Methemoglobinemia and Hemolytic Anemia

Two cases that have recently been observed showed both acquired hemolytic anemia and intracellular methemoglobinemia.[118, 119] The absence of gastrointestinal disease and of drug intake excludes the types of secondary methemoglobinemia mentioned above. The patients' erythrocytes also functioned normally in reverting methemoglobin. Although no cause has been discovered, it is conceivable that some endogenous substance is responsible for both oxidation of the hemoglobin and red-cell destruction.

Therapeutic Use of Methemoglobin

Methemoglobin is of no value in carbon monoxide poisoning but is useful in combating cyanide. Cyanide produces paralysis of tissue respiration by combining with cytochromes. It is possible to reduce its toxicity by the production of methemoglobin, for which cyanide has an even greater affinity. When methemoglobin is produced prophylactically, animals are protected against several times the lethal dose of cyanide.[120–123] Even when given after exposure to cyanide, methemoglobin may successfully compete with the ferricytochrome oxidase for the cyanide ion.[124] The usual therapeutic regime consists of 0.5 gm. of sodium nitrite intravenously over five to ten minutes, followed by 25 gm. of sodium thiosulfate intravenously for ten minutes. The latter combines with the cyanide to form thiocyanate, which is relatively nontoxic and is

excreted.[25] Inhalation of amyl nitrite is even more rapid in its antidotal action.

Sulfhemoglobinemia

Sulfhemoglobin is an abnormal pigment, not found in the body under ordinary circumstances. It exists exclusively inside the red cell except in cases of sulfhemoglobinemia with associated hemolysis.[115] The exact nature of sulfhemoglobin is unknown, but available evidence indicates that there is a closed porphyrin ring with no increase in easily split iron.[126] It is to be distinguished from choleglobins.[127] The latter are open ring structures and a biproduct of sulfhemoglobin formation by hydrogen sulfide in vitro. They have not been demonstrated in man. It is possible that the transformation to sulfhemoglobin is the result of displacement of one of the N atoms in the pyrol ring by sulfur.[128] Although it has not been prepared in pure form, its spectrum shows a strong band at 618 (Fig. 4), which has been the basis of spectroscopic and colorimetric methods of identification.[8, 11, 129] It can be qualitatively identified with a hand spectroscope since its band is unaffected by potassium cyanide, but is dispersed by hydrogen peroxide.[2, 8, 9]

The formation of sulfhemoglobin does not indicate cell damage, but does represent an irreversible change in hemoglobin pigment. In workers who became cyanotic from exposure to trinitrotoluene, the disappearance of sulfhemoglobin was identical to the disappearance rate of transfused normal erythrocytes as determined by Ashby counts.[130] The life span of the involved cells was not altered. Thus, whereas methemoglobin due to drugs rapidly reverts, sulfhemoglobinemia is a stable compound cleared from the blood over as long as three or four months. Although hemoglobin is rendered inert as an oxygen carrier, it seems unlikely that sufficient amounts of sulfhemoglobin are ever produced clinically to endanger the life of the patient.

Clinical Sulfhemoglobinemia

That Due to Drugs

Drugs causing sulfhemoglobinemia include the group described above as methemoglobin producers (Table 1). There are frequent reports of its production by the earlier sulfonamide derivatives,[91] by phenacetin and acetanilid[101] and by aniline.[97] Oxidizing agents, such as phenyl hydrazine, hydroxylamine and paraminophenol, catalyze the production of sulfhemoglobin in vitro.[8] Similarly, the clinical conditions necessary to produce sulfhemoglobin are an oxidizing drug and either constipation or a sulfur-containing medication.[131] It should not be inferred that methemoglobin is an intermediary leading to sulfhemoglobinemia, since cases of congenital methemoglobinemia have not had sulfhemoglobinemia. Once formed, there is no way to rid the blood stream of sulfhemoglobin other than by actually removing blood. Treatment consists of removing the drug and intestinal conditions causing the disorder.

Enterogenous Sulfhemoglobinemia

In reviewing cases of enterogenous cyanosis, one is impressed by the greater frequency of cases of sulfhemoglobinemia[115, 132–142] and by the predominance of constipation in these patients as compared

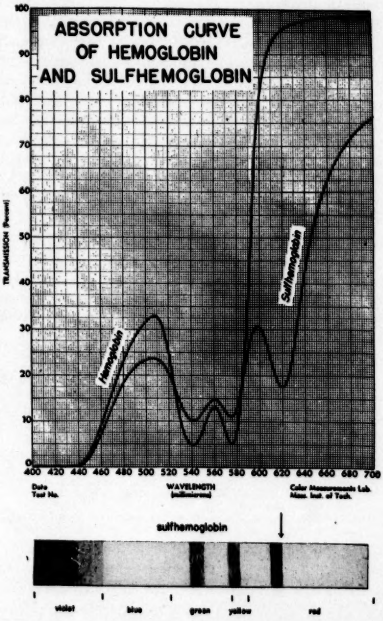

FIGURE 4. *Spectrophotometric Absorption of Sulfhemoglobin. In the upper portion the percentage transmission of a solution of oxyhemoglobin is compared with that of a solution of sulfhemoglobin and hemoglobin. There is a strong absorption of the sulfhemoglobin solution at 620 millimicrons. The greater intensity of sulfhemoglobin is seen by a comparison with Figure 1. Both solutions had approximately the same amount of abnormal pigment. The absorption band of sulfhemoglobin in the red of the spectrum as seen in the hand spectroscope is shown below.*

with diarrhea in patients with enterogenous methemoglobinemia. The importance of disturbed bowel function is well shown by the case of a nine-year-old boy reported by van den Bergh[110] with a rectal stricture and cyanosis for two years. After operation with relief of the obstruction, the cyanosis disappeared. Symptoms are identical to those with enterogenous methemoglobinemia, the only clinical differentiation being the much slower rate of dis-

appearance of the cyanosis. As pointed out by van Lier many patients reported had been taking aniline derivatives, which he and others[82, 115, 132] demonstrated to be capable of producing sulfhemoglobin in the presence of constipation.

Summary

Abnormal hemoglobin pigments may be suspected in patients by the recognizable clinical syndrome in the congenital enterogenous types, by a history of drug intake or by the very intensity of the cyanosis with minimal symptoms. The diagnosis depends on the spectroscopic identification of the abnormal pigment. Methemoglobinemia may be due to dysfunction of the normal red-cell reconversion mechanism or to conversion of hemoglobin by circulating oxidants. Treatment with methylene blue or ascorbic acid depends on the etiology of the methemoglobinemia, since ascorbic acid is effective only in congenital methemoglobinemia.

Sulfhemoglobin is formed by the action of a methemoglobin-producing drug in addition to either constipation or a sulfur-containing medication. Unlike methemoglobin, which may be reverted rapidly to hemoglobin, sulfhemoglobin once formed remains until the red cell containing it is destroyed.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 34391

PRESENTATION OF CASE

A fifty-nine-year-old woman entered the hospital because of anorexia, nausea and vomiting.

The patient was essentially well except for "indigestion" following meals until seven months before admission, when she had an illness lasting three weeks characterized by cough and severe left pleural pain. A short time following this her gall bladder was removed at a community hospital following an attack of anorexia, nausea and vomiting. The gall bladder was said to be perforated, with localized peritonitis. At that time, because of an enlarged heart and slight dyspnea on exertion, she was digitalized and continued to take the drug (one pill a day) until admission. Following operation she did not do well, being bothered by anorexia, progressive weakness, fatigue, dyspnea on exertion and afternoon ankle swelling. She had two short episodes of fever without chills and "stomach spells" occurring approximately every third day for the six months prior to admission and consisting of nausea, belching and vomiting of thick, green material. There was never any blood in the vomitus, and she never had any abdominal pain. She also noted one to three loose, watery bowel movements a day without blood, pus or cramps, the bowel habits having previously been normal and the stools formed. She lost 30 pounds of weight during the present illness.

Physical examination showed an emaciated, pale woman. The thyroid gland was not palpable. The neck veins were distended with the patient 15° above the horizontal position. The chest was emphysematous but clear. The heart seemed enlarged to percussion, the rhythm was regular, with occasional extrasystoles, and there was a Grade II systolic murmur along the left sternal border. The liver edge was felt four fingerbreadths below the costal margin.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 4,900,000, with a hemoglobin of 13 gm. per 100 cc., and a white-cell count of 7500, with 74 per cent neutrophils. Two stool specimens were guaiac negative. The arm-to-tongue circulation time was 35 seconds, and the venous pressure was equivalent to 140 mm. of water. An x-ray film of the chest disclosed a heart enlarged in all chambers, with a suggestion of left ventricular predominance. The lung markings were slightly increased, and there was a small amount of fluid in the left pleural sinus. An electrocardiogram showed apparent auricular fibrillation, with a rate of 85, small Q waves in Leads 2 and 3, depressed ST segments in Leads 1, 2 and CF_5, flat T waves in Leads 1, 2, 3, CF_2 and CF_4, a diphasic T wave in Lead CF_5 and a tendency to low voltage. The QRS interval was 0.10 to 0.12 second. A gastrointestinal series was negative. The van den Bergh reaction was 1.4 mg. per 100 cc. direct, and 1.6 mg. indirect, the cephalin-flocculation test was + in twenty-four and ++ in forty-eight hours, and the prothrombin time was normal.

During the hospital stay there was an irregular fever, the temperature going as high as 101°F. During the seventh day a slight hemoptysis occurred. Fine rales were heard at the right base, and a film of the chest showed an area consistent with infarct. Heparin and dicumarol were started, but on the tenth day femoral-vein interruption was decided upon as a more permanent form of therapy. Large doses of vitamin K were given. On the following day there was a short episode of

dyspnea and cyanosis, with nausea and vomiting but no chest pain or cough. The patient was taken immediately to the operating room. The right superficial femoral vein was ligated and divided without incident. No clot was found. The vein on the left side was exposed, found to be free of clot, and was about to be opened when the patient suddenly became cyanotic and dyspneic and died.

Differential Diagnosis

Dr. Richard J. Clark: Let us go briefly over this history again. The patient apparently had indigestion for a somewhat indefinite period, which in view of later events, may reasonably have been attributable to chronic gall-bladder disease. Seven months before entry she had a briefly described illness of three weeks' duration characterized by cough and severe left pleural pain. We wonder about the possibility of bronchopneumonia or pulmonary infarction at that time. We may question a myocardial infarction in view of later events; certainly, the description is not characteristic of any such episode although it has to be borne in mind.

She soon had a severe attack of anorexia, nausea and vomiting, following which a cholecystectomy was done. There is the helpful point that the gall bladder was found to be perforated. We know that there was definite gall-bladder disease with some element of infection and that the difficulty in the gastrointestinal system was not all secondary to cardiovascular disease. We are not told whether gallstones were present or exactly what was done: whether the common duct was explored, or whether or not it was drained.

At the same point in the history cardiac enlargement was noted. This is the first indication that cardiovascular disease was present. Following operation the patient did poorly and had increasing signs of gastrointestinal disturbance and apparently some evidence of decreasing cardiac reserve. There were two short episodes of fever without chills, but they are not sufficiently well described to enable us to draw any definite conclusions from them. The loose bowel movements might make one wonder if there were any involvement of the pancreas along with biliary-tract disease, but there is nothing in the protocol on which I can base any such diagnosis. We are told that the gastrointestinal series was negative and that two stool examinations were negative. These factors are against any intrinsic disease of the stomach or bowel. The loss of weight is explainable on the basis of the repeated gastrointestinal upsets and anorexia.

On entry there was evidence of an abnormal heart, which appeared to be in borderline failure, and also of an enlarged liver. While in the hospital the patient had an irregular fever of moderate degree. On the seventh day there occurred an episode strongly suggesting pulmonary infarction. Subsequently, in the process of bilateral femoral-vein ligation, the patient died suddenly.

The problems here are threefold. What was going on in the biliary tract, what was the cardiac lesion, and what was the terminal event? So far as the biliary tract is concerned she had had persistent gastric symptoms since the cholecystectomy and showed an enlarged liver on physical examination. We are not told whether the liver was tender or anything else regarding its character. Nothing is said about clinically detectable jaundice, and there is no report of the urinary findings. She had an abnormal biphasic van den Bergh reaction of slight degree. The cephalin-flocculation reaction was insignificant, and the prothrombin time normal. Apparently she had no serious liver disturbance. We might wonder about a residual stone in the common duct, causing intermittent biliary obstruction. If so, we would expect more evidence of jaundice and also a history of some abdominal pain and colic. What about hepatic abscess of some type, secondary to biliary-tract infection? Had this been present we would have expected a more fulminating course and a higher white-cell count and a febrile reaction at the time. I rule out a malignant lesion for lack of more specific evidence. Hepatic congestion, secondary to cardiac disease, is to be considered, but I doubt this because of the long-continued symptomatology without other significant evidence of congestive failure. A low-grade ascending cholangitis, which had carried on since the time of the cholecystectomy, might explain this phase of our problem most satisfactorily.

Next to consider is the cardiac lesion. May we see the films at this point?

Dr. Stanley M. Wyman: The heart is described as grossly enlarged, the borders extending to both the right and the left, more markedly toward the left. There is a faint suggestion that the left mainstem bronchus is elevated. In the lateral view there is some prominence of the upper posterior heart border, suggesting left auricular enlargement. The heart extends well to the anterior chest wall, which makes one suspect that in addition to left ventricular enlargement there is probably right ventricular enlargement. The pulmonary vascular shadows are not definitely abnormal. There is some fluid in the left costophrenic sinus laterally. The second examination, done about a week after the first, shows an area of hazy, indefinite density in the right lower-lung field, seen to lie posteriorly against the chest wall. This is the shadow interpreted as being consistent with infarct.

Dr. Clark: There is some unusual prominence in the region of the pulmonary conus, is there not?

Dr. Wyman: The left upper border of the heart I would not interpret as being prominent. I think the pulmonary artery is probably engorged but may be overlain by the heart shadow per se. The

descending aorta is not remarkable. There is some calcification in the aortic arch.

DR. CLARK: There is no evidence of old pleurisy on the right?

DR. WYMAN: Not on the original examination. The right leaf of the diaphragm and the costophrenic angle are clear. The stomach and the duodenum appear grossly normal.

DR. CLARK: There is no evidence of gallstones in the region of the gall bladder?

DR. WYMAN: I do not have a film that includes the right upper quadrant adequately. I do not see any here.

DR. CLARK: I gather, then, that this heart shows more generalized chamber enlargement than is ordinarily seen in coronary-artery disease. Is that correct?

DR. WYMAN: Yes. It did not make me think of coronary disease primarily.

DR. CLARK: The electrocardiogram as described suggests coronary disease, digitalis effect or some diffuse myocardial process. May I see a print of the tracing? This shows a normal axis with a low QRS complex in Lead 1. There are no visible P waves. The T waves throughout are low to flat. I would not consider the Q waves in Leads 2 and 3 sufficiently prominent to be significant. The QRS complexes are slightly widened.

Could this patient have had valvular heart disease? Aortic stenosis might be suggested by the Grade II systolic murmur along the left sternal border, but this alone is insufficient evidence for such a diagnosis. Viewing the x-ray films and observing suggestive left auricular enlargement we wonder about mitral disease. The murmur of mitral stenosis may be undetected, but all in all, I cannot diagnose this or any other valvular lesion.

What about hypertensive heart disease on the basis of a previously elevated blood pressure? I rule this out because of the history and the lack of any good cardiographic evidence; low voltage and absence of left-axis deviation are strong counter-evidence.

If we are to assume recurrent pulmonary infarction, could the patient have had cor pulmonale? The electrocardiogram is not in keeping, nor would this explain left-sided cardiac enlargement.

Certain rarer forms of diffuse myocardial involvement are to be considered. The generalized chamber enlargement, the continued suggestion of right-sided heart failure, the low voltage and the multiple T-wave involvement are all consistent. This patient with chronic anorexia and gastrointestinal disturbance might well have had avitaminosis; beriberi heart disease comes to mind, but in this condition the circulation time is characteristically rapid with failure, whereas here there was a prolonged circulation time. I see no good evidence for myxedema or myxedema heart in spite of the low voltage. The distinct possibility of an idiopathic myocarditis, such as a Fiedler's, is to be seriously thought of in a situation of this type. This diagnosis is made primarily by the exclusion of other possibilities. I came here prepared to make a diagnosis of old coronary-artery disease, being influenced especially by the Q waves in Leads 2 and 3 reported in the protocol, but these we have seen to be rather insignificant. The complete lack of cardiac pain is against this diagnosis, as is the appearance of the x-ray film. I shall, therefore, put down a diffuse nonspecific myocarditis, possibly a Fiedler's, as my first bet, leaving coronary-artery disease as second choice.

Finally, let us view the pulmonary condition and terminal events. I am intrigued with the x-ray finding of fluid at the left base and none on the right. Unilateral left pleural effusion from cardiac failure has been shown to be rare unless the right pleural cavity is obliterated by adhesions. It is usually due to some local cause such as pleurisy, secondary to pulmonary infarction. Almost certainly this patient had a pulmonary infarction on the seventh hospital day and another a few days later after anticoagulant treatment, which was followed by vitamin K preparatory to venous ligation.

We are given no localizing evidence in the protocol to incriminate the legs. Obviously the Surgical Service suspected femoral phlebitis since they went ahead with ligation, and on the basis of statistics this is the most likely source for the emboli. We are told that no evidence of clot was found on opening the right vein, and this was divided. No clot was noted on the left, but death occurred before the vein was opened; presumably a clot may have slipped up from below during manipulation. A second possible source of emboli may have been from mural thrombosis in the right side of the heart, which we were told was fibrillating, but we would hardly expect such a thrombosis alone to give rise to a sudden fatal embolism. In any event I believe that we shall find evidence of multiple old and new pulmonary infarcts and that the terminal event was a massive pulmonary embolism.

DR. TRACY B. MALLORY: Dr. Taylor, I believe you saw this woman. Would you tell us what you thought about the case?

DR. ISAAC TAYLOR: When this patient came in the question arose whether she had residual sepsis in the biliary tract or carcinoma of the stomach primarily. Because of the pulmonary infarct as described in the protocol our attention was focused in that direction. We were concerned at the same time with the treatment of congestive failure, which was brought under control. Then, as one gathers from the protocol, there was some discussion regarding how to treat this woman. She was started on anticoagulants after a couple of days on the basis of the apparently poor cardiac status; she was having a restricted life, and we changed our plans

and decided on venous ligation. We stopped the anticoagulants. On the morning of death there was an episode that seemed most likely another pulmonary infarct, so that we hurried with the venous ligation. There was no evidence at any time that she had active phlebitis in the lower extremities. We made the decision to ligate the femoral veins on a statistical basis.

DR. MALLORY: Dr. Means, would you like to give your opinion now or reserve it until later?

DR. JAMES H. MEANS: I remember this patient very vividly, and the case caused me a certain amount of emotion. I will tell you why in a moment. I took the Medical Service over the day after she came in. They had done a great deal of work on her. Dr. Taylor has given an outline of what happened. They had just about disposed of the abdominal possibilities at that time, and attention was focused on the heart as probably the most important feature. I wrote, "I think the whole picture can be explained on the basis of low-grade, chronic congestive heart failure, probably arteriosclerotic. I assume that is synonymous with coronary-artery disease. I suppose the indication now is to digitalize." Then I began to think more about the x-ray picture, indicating pulmonary infarction, and concluded that we ought to do something about that. Dr. Dahl, as I recall, favored putting the patient on anticoagulants. She got heparin first and dicumarol afterward. We have heard so much of how to treat phlebitis that there is a great deal of confusion in the professional mind about anticoagulants versus ligation. I suppose it was because I was on dicumarol myself, having had phlebitis recently, and my medical brethren were curing me in that way, that this case was very vivid to me. We put her on these anticoagulants, but I was still worried about whether she was the type of patient that should be put on anticoagulants or ligated. My thinking was conditioned a little bit by the fact that I had escaped, up to that point, getting ligation myself and I hated to wish it on her. Dr. Paul D. White says here, "This is the wrong kind of patient to treat with anticoagulants." It is all right to treat a vigorous fellow like me with anticoagulants, but he advised that this bedridden cardiac patient should be ligated, and I bowed to his superior wisdom. The only trouble was that we had prolonged her prothrombin time by then, and we had to give her vitamin K to shorten it. Then the surgeons took over, and she died on the table before they could ligate. I therefore think that we had grossly mismanaged this case. I felt sorry about that. I will let Dr. Mallory tell us what was actually found.

DR. MALLORY: Have you an opinion, Dr. Zamecnik?

DR. PAUL C. ZAMECNIK: I saw the patient when she first came in and was taken in by the possibility that the gastrointestinal symptoms were the most prominent feature of the history. We considered carcinoma of the stomach as a possibility. The negative gastrointestinal series then disillusioned us and caused us to pay more attention to the cardiac status.

CLINICAL DIAGNOSES

Pulmonary infarction.
Phlebothrombosis.
Arteriosclerotic heart disease.

DR. CLARK'S DIAGNOSES

Idiopathic myocarditis or coronary-artery disease.
Pulmonary infarcts, recent and old.
Terminal pulmonary embolism.

ANATOMICAL DIAGNOSES

Coronary thrombosis, recent.
Myocardial infarction, recent.
Mural thrombi, right ventricle and left auricle.
Pulmonary infarcts, recent and old.
Coronary sclerosis, severe.
Cardiac hypertrophy and dilatation.
Cerebral lateral-sinus thrombosis, left.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed no massive pulmonary embolism. There were numerous infarcts of the lung in both lower lobes of varying ages. Some of them were dense, old, fibrous scars, some were of intermediate age, and one was very fresh. The heart was diffusely dilated and moderately hypertrophied. There were no valvular lesions. We found thrombi in the right ventricle and also in the left auricle. There was a large area of infarction at the apex of the heart involving the interventricular septum, and I think the right ventricular thrombi were unquestionably secondary to that. So we had an intracardiac source, as Dr.

Clark suggested as a remote possibility, for the pulmonary infarct.

The gall bladder had been removed. We found nothing wrong with the biliary tract. The liver showed only a severe grade of chronic passive congestion. A careful search of all the ligated veins showed not the slightest trace of thrombosis above or below the ligature on either side. One other possible source of embolism is the cerebral left lateral sinus, which was extensively thrombosed, and it is conceivable, although unlikely, that the thrombus had broken loose from there. The coronary arteries showed a very old, calcified occlusion of the left descending branch, considerable sclerosis and a very fresh thrombus of the right circumflex. So death was due, I think without question, to sudden coronary occlusion, not to pulmonary embolism.

DR. CLARK: How often do you see pulmonary infarcts coming from intracardiac thrombi?

DR. MALLORY: We see them with significant frequency in valvular heart disease. They are quite uncommon in coronary-artery disease. Thrombi in the left ventricle, of course, are the rule in cardiac infarction, but we see them only occasionally in the right ventricle. Usually when a thrombus is present in the right ventricle it is secondary to an infarct of the interventricular septum, and thrombi will be found in both ventricles.

DR. CLARK: We have recently seen 2 cases of pulmonary infarction in which the evidence was strongly suggestive of an intracardiac source of the emboli. The possibility of this mechanism is of great importance in reaching a decision regarding anticoagulant versus ligation therapy.

DR. MALLORY: One can raise the point whether it is wise to give dicumarol with fresh infarction of the heart. It is quite possible that the mural thrombus, which forms over an area of infarction, tends to reinforce the cardiac wall, at that point, a process that might be prevented by the dicumarol.

DR. CLARK: I have recently seen a case of myocardial infarction treated with dicumarol in which the patient died of myocardial rupture on the eighteenth day — rather later than the average rupture. Possibly the lack of mural thrombosis was the cause.

DR. MEANS: Dr. Clark gave a scholarly dissertation, but there is one statement that he made on which I would like to comment. He seemed to view with some surprise the fact that nothing was found when the femoral veins were opened. I think that is common. I am sorry Dr. Linton is not here, but I get the impression from him that he often opens the veins when there is unquestionable thrombosis below and finds them quite empty. I do not think that the fact that they were empty is significant. Taking all the cases of pulmonary embolism with infarction, what percentage would you say come from the heart?

DR. MALLORY: What would your opinion be, Dr. Castleman?

DR. BENJAMIN CASTLEMAN: Probably about 95 per cent.

CASE 34392

PRESENTATION OF CASE

A thirty-nine-year-old salesman was admitted to the hospital because of cough and sweating.

The patient was more or less well until approximately seven months before entry, when, following a cold, he noted severe cough productive of foul sputum. The cough became progressively worse and was accompanied by night sweats and increasing dyspnea. Approximately five months after the onset of symptoms his condition became so bad that he had to stop work. He consulted a physician, who took a roentgenogram of the chest and had him admitted to a community hospital. Here he was given penicillin for ten days, after which the cough and dyspnea nearly disappeared. However, shortly before his anticipated discharge he began to have transient pain in the middle of the right side of the chest posteriorly. Since that time he had increase in cough as well as a feeling of pressure over the right side of the chest anteriorly. He never had hemoptysis.

The patient was a healthy child and had no serious illnesses. However, he stated that he had always become dyspneic on exertion and that during the past ten years he had been nervous and just "not well." Two years before entry he was found to have a duodenal ulcer by roentgenogram. He had slight abdominal pain recently and almost daily had tarry stools for an unknown length of time. He had had two "nervous breakdowns" in past years. He smoked two packages of cigarettes daily and more recently had been drinking a fair amount about every other day.

Physical examination revealed a well developed, well nourished man in no acute discomfort, but having a nonproductive cough. There was an area of dullness with normal breath sounds in the midportion of the right side of the chest anteriorly. There was clubbing of the fingertips with questionable clubbing of the toes. The left Achilles jerk was absent.

The temperature was 98.6°F., the pulse 90, and the respirations 20 per minute.

The white-cell count was 17,600, with 75 per cent neutrophils, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The hemoglobin was 15.1 gm. The urine was normal.

An x-ray film of the chest showed an area of segmental atelectasis in the right upper lobe, which involved chiefly the anterolateral portion of the lobe (Fig. 1). The lung was particularly dense laterally and showed a mottled appearance more medially. A definite mass was not identified, and the bronchial tree, so far as visualized on the right, was within normal limits. No definite adenopathy was observed although there was a vague density in the right paratracheal region. Comparison of the roentgenograms taken over a two-week period during the second month prior to admission showed the appearance of the lungs to be about the same, although in the present examination the lateral density was slightly greater. A gastrointestinal series was negative. There was no evidence of a filling defect or ulcer.

Three days after admission bronchoscopy was done with a report of "considerable mucopurulent sputum from the right upper lobe and moderate inflammatory changes in that orifice, mild changes in the rest of the right main bronchus, and a normal carina and left bronchial tree — the findings are consistent with inflammatory disease of the right upper lobe; no neoplasm is seen."

Smears were taken by bronchial lavage of the right main bronchus for cytologic examination. These were reported negative.

A culture of sputum was reported to have alpha-hemolytic streptococci as the predominating organism and was negative for beta streptococcus and pneumococcus. No acid-fast bacilli were seen in the sputum.

The highest temperature recorded during the week after admission was 99°F. Usually, it was normal or subnormal.

On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. Allen G. Brailey: Let us look at the x-ray films.

Dr. Stanley M. Wyman: The minor septum is arched somewhat upward and is particularly well seen in the lateral view, having a rather high bend

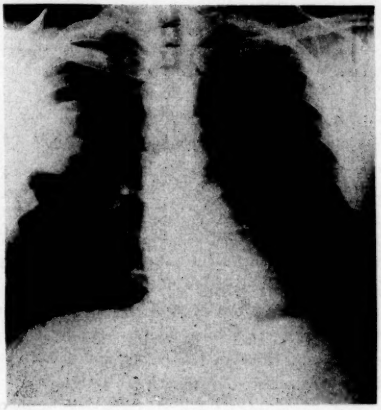

Figure 1.

posteriorly and laterally. There is an area of rather indefinite density in this portion of the upper lobe, the density extending posteriorly and toward the hilus. There is a suggestion of a very poorly defined section of central rarefaction in this area, measuring about 3 cm. in diameter. This cannot be identified in the lateral view because the film is not adequately exposed. The bronchus to the right upper lobe can be seen for a short distance and appears grossly normal. There is no appreciable fluid in either pleural cavity, but there is a suggestion of some pleural reaction overlying the right upper lobe laterally. I am not much impressed by the density described in the right mediastinum laterally. The examination on the gastrointestinal series is reported as being negative and I cannot see any gross disease. The duodenal cap is not well outlined.

DR. BRAILEY: Why do you say atelectasis? Why not just consolidation?

DR. WYMAN: The position of the septum indicates some collapse of a portion of the upper lobe. The septum is displaced upward, out of the normal situation.

DR. BRAILEY: Is there any x-ray evidence to indicate whether or not air is going into that part of the lobe?

DR. WYMAN: No x-ray evidence, except that there is atelectasis. Presumably there is peripheral disease; whether or not it is due to bronchial plugging, I cannot say.

DR. BRAILEY: This process is in the upper lobe?

DR. WYMAN: Yes, entirely in the upper lobe.

DR. BRAILEY: The problem presented by this patient is defined rather sharply in the history. He was an unstable, ill adjusted person, to be sure, but he had an organic disease process as well, which appeared to be confined to the chest — in fact, to the anterolateral division of the right main bronchus. The evidence given implies an obstructive lesion of the bronchus in question, with atelectasis and some degree of infection distal thereto. Such an obstruction might be produced by any one of three things: foreign body, an inflammatory process or neoplasm. Foreign body does not need to be seriously considered, I think. An adult who has inhaled a foreign body will surely be able to give a vivid account of the time, place and circumstances under which it occurred.

The question that gives this history a lively interest is whether the bronchial obstruction was inflammatory or neoplastic, or, more exactly, whether it was tuberculous or neoplastic, since the odds are overwhelming that if the stenosis was the result of inflammation, the inflammation was endobronchial tuberculosis. What scraps of evidence in favor of tuberculosis can we dig up? At thirty-nine years the patient was a relatively young man, and furthermore he offered the information that for ten years he had not considered himself really well. Perhaps he was trying to describe the unexplained fatigability and lassitude that are often early signs of tuberculosis. The x-ray picture is not typical of tuberculosis, but neither is it inconsistent.

Do you agree that it is not inconsistent with tuberculosis, Dr. Wyman?

DR. WYMAN: I agree; it is not inconsistent with it.

DR. BRAILEY: But certainly if he had acid-fast bacilli of any considerable duration, the disease was an unusually benign and smoldering affair. He had had no hemoptysis. He seems to have had little fever. Nothing is said of weight loss, and finally no acid-fast bacilli were seen in the sputum. We are not told whether this was a single routine examination or whether the sputum was concentrated. Nevertheless, acid-fast bacilli are apt to be found easily in the sputum of patients with endobronchial disease and, therefore, some importance must be attached to the statement that they were not found in this case even though the search may have been casual.

In weighing the evidence for neoplasm one should consider adenoma first. Ten per cent of all pulmonary tumors are adenomas of the bronchi, and the great majority occur in persons under forty years of age. They typically produce obstruction with drowned lung upstream from the dam. On the other hand, they are prone to bleed, and this man raised no blood. Still worse, they occur almost exclusively in main-stem bronchi and are readily seen by the bronchoscopist whereas the lesion in this case could not be seen.

The only other obstructive lesion we need to consider seriously is carcinoma of the bronchus. It is the commonest pulmonary tumor, although it is true that only 10 to 15 per cent of such carcinomas occur in men as young as this patient. It usually arises in main-stem bronchi, but 25 per cent develop sufficiently remote from the trachea not to be visible by bronchoscope. The presenting symptom is characteristically a harassing and persistent cough, followed by dyspnea and later other signs, such as pain, hemoptysis and weight loss. This patient had clubbing of the fingers. The physiology of clubbing is still poorly understood, but it is a fact that clubbing frequently occurs in persons with carcinoma of the bronchus whereas it is a rather rare sign in tuberculosis. Against cancer we have a negative cytologic smear, but I do not believe that we can allow ourselves much reassurance on that account.

Judgment is difficult as Hippocrates warned. I would like a much more careful search for tubercle bacilli, but I am going to assume that the patient did not have tuberculosis. Obviously he was a

rather neurotic person with a history of "nervous breakdowns," requiring forty cigarettes a day and capable of describing normal stools as tarry. I think his alleged ill health of ten years' duration was only evidence of maladjustment. I think it is better judgment to guess that he had a cancer of the bronchus of a few months' duration, which produced early obstruction and which should have been easily resectable.

DR. WYMAN: Could this have been purely an inflammatory process such as a solitary lung abscess, Dr. Brailey?

DR. BRAILEY: I do not see why not. You did not say he had an abscess until just now. Furthermore, an abscess certainly could arise *de novo* with no obvious excuse. But the film suggests that the bronchus was plugged and that the abscess was secondary to plugging. I think the important thing is not whether the patient had an abscess but why the bronchus was stenosed.

DR. WYMAN: From the x-ray point of view this could be a peripheral tumor or inflammation. The area of rarefaction could be an abscess cavity or cavitation in tumor. It is poorly seen on these films, however.

DR. DONALD S. KING. As we watched this patient preoperatively we came to the conclusion that the process in the lung was due to a chronic nontuberculous infection rather than tuberculosis or infection secondary to a bronchial tumor. At one time he had had definite foul sputum, but this persisted for only a short time and in general the cough and sputum became less troublesome rather than more so. Besides this we had the evidence of a negative bronchoscopy and a negative examination of bronchial secretion for tumor cells. Nevertheless, the x-ray densities persisted, and we believed that exploratory operation was definitely indicated.

CLINICAL DIAGNOSIS

Chronic nontuberculous pulmonary infection.

DR. BRAILEY'S DIAGNOSIS

Carcinoma of bronchus.

ANATOMICAL DIAGNOSIS

Lung abscess.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The surgeon removed the right upper lobe. On cutting through the lobe it was found to be slightly smaller than normal and very heavy, with very little air anywhere in the lobe. On section, there was a collapsed cavity 7 cm. in diameter, and the surrounding area was atelectatic. Microscopical examination showed no evidence of tumor but a chronic inflammatory process, the center of which showed acute inflammation with necrosis. Surrounding it was a great deal of necrosis with destruction of the alveolar walls. So I think we have to assume that this was a chronic lung abscess, etiology undetermined.

DR. BRAILEY: It started out with upper respiratory infection?

DR. CASTLEMAN: Yes.

DR. KING: Because the patient was of a very nervous disposition we anticipated a stormy convalescence but were happily surprised to find that he had very little postoperative difficulty and could be discharged just a little less than two weeks after the lobectomy. He was still worried about all sorts of extrapulmonary symptoms, but I believe that the pulmonary condition has been cured.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

POPULATION TRENDS

ENGLAND has become so alarmed over her trend toward an aging and declining population, that four years ago the Coalition Government appointed a Royal Commission to study the problem. For sixty years the birth rate had been falling, but also the country had known demoralizing unemployment, resulting in a paradoxical and disturbing state of affairs. Concerned as the kingdom was over its declining population it could not adequately care for what it had.

Immediately on appointment of the Commission, according to *The Lancet**, the birth rate suddenly rose "impishly and awkwardly" to confuse the planners and becloud the issue. This rise was not sustained. The rate again started downward, perhaps because the Government had given the family man a woefully inadequate relief in taxes to compensate for his increased expenses.

*Leading Article. Population policy? *Lancet* 1:717, 1948.

In general, reactions toward population trends are hardly consistent with the apparent facts. Politicians, with a nearly pathologic fervor, crave large populations, viewing them, apparently, almost in the light of standing armies despite the inevitable consequences, sooner or later, of unemployment, poverty and discontent. Yet even from a military standpoint large populations are not necessarily the important factor in a nation's greatness. Certainly in some of the countries of Asia, the most heavily populated in the world, numbers have proved to be no asset from any angle.

This much must be conceded. Declining population levels are frequently a sign of decadence. They mark the turning point of nations that have passed their peak in expansion, in strength and in character, and are substituting for a waning national ambition an attempt — that has always proved eventually vain — to consolidate their gains, rest on their laurels, withdraw behind their defenses and exist in comfort and security.

The aggressive behavior that results in wars between nations represents to many persons an intolerably nationalistic attitude, but the fact remains that when a species or a nation or a person is forward bound and headed toward some destined goal, aggressiveness, and in the instance of the first two, growth, are of the essence of their strength.

Population, however, while it tends to increase as a nation struggles into the sun, does not provide the best answer to the problem of prolonged survival. The spirit of a people is more important than its numbers. Population trends are important only as they indicate a nation's spirit of survival, or its loss. And without that spirit no economy, however well planned, can long be successful.

CENTENNIAL OF THE MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA

ELSEWHERE in this issue of the *Journal* attention is called to the centennial celebration of the founding of the Medical Society of the State of Pennsylvania in Philadelphia from October 3 to 7.

An interesting scientific and social program has been arranged for the meeting.

The organization of the society followed close on the heels of the first meeting of the American Medical Association in 1847. In December of that year representatives of the Chester County Medical Society, believing that physicians should organize on a state-wide basis, met in Lancaster, where the following resolution, proposed by Dr. Wilmer Worthington, later president of the State Society, was adopted:

> Whereas no State Medical Society exists in Pennsylvania; and believing that such an institution would greatly contribute to the advancement of medical knowledge within its bounds,
>
> Therefore, *Resolved*, that it is expedient to hold a convention at such time and place as may be hereafter agreed upon. . . to effect such permanent organization as may be deemed best suited to accomplish the object in view. . . .[1]

The Lancaster County Medical Society concurred in this resolution, and in April, 1848, "gathered the men who organized the Medical Society of the State of Pennsylvania."[1]

The *Journal* extends heartiest congratulations to the Pennsylvania physicians and expresses the hope that the centennial celebration will be as successful and pleasant as the fiftieth anniversary in 1898, for which it had been announced that Lancaster County Medical Society was "prepared to 'set out barrels and barrels of pretzels.' "[2]

References

1. Editorial. Founding of State Medical Society. *Pennsylvania M. J.* 1:328, 1898.
2. Editorial. Next meeting of State Society and its scientific program. *Pennsylvania M. J.* 1:416, 1898.

PUBLIC HEALTH AND THE DISEASES OF OLD AGE

One of the recent Saturday morning sessions of the Health Forum conducted by the Harvard School of Public Health was devoted to a discussion of public health and diseases of old age by Louis I. Dublin, chief statistician for the Metropolitan Life Insurance Company.* In his address Dr. Dublin pointed out the marked change that the mortality picture in this country has undergone since the turn of the century. The basic shift has been in the direction of greatly increasing the importance of the diseases of later life. These changes, he noted, have been brought about by two major developments: the extraordinary success achieved by medical science and public-health administration in the control of infectious diseases; and the progressive aging of the population. The indications are that these trends will continue.

Dr. Dublin called attention to the striking change that the age structure of the population is undergoing. In 1900, only 4.1 per cent of the population of this country was sixty-five years or older; by 1940, the proportion increased to 6.8 per cent, and it is estimated that by 1960 more than 9 per cent, and by the turn of the century more than 13 per cent of the population will be in this old-age bracket. The actual numbers involved are even more impressive. In 1900 there were about 3,000,000 people in the United States who were sixty-five or older; in 1940 the number in this age group, increased to nearly 9,000,000, and by 1960 their total is expected to reach 14,000,000 and by the end of the century 21,500,000.

Accompanying this change in age distribution of population, there are parallel changes in the ranking of the leading causes of death. In 1900 the first ten causes of death were tuberculosis, pneumonia, diarrhea and enteritis, heart disease, nephritis, accidents and violence, cerebral hemorrhage, cancer, bronchitis and diphtheria, in that order. By 1940, diseases of the heart, cancer, accidents and violence, cerebral hemorrhage and nephritis were the five leading causes of death, and pneumonia, tuberculosis, premature birth, diabetes and arteriosclerosis followed in that order. Thus of the ten principal causes of death at present only one is concentrated in early life; the others either show a heavy concentration in later life or have the highest death rates in the older age groups.

The data that Dr. Dublin brought out indicate the need for a reorientation in the point of view and in the activities of social and welfare agencies, health officers and physicians to meet the changing needs of their communities. The public-health and medical professions, he believes, have largely solved the major problems of sanitation and communicable-disease control and should now be prepared to

*Public health and disease of old age. (Summary.) *Statist. Bull. Metrop. Life Ins. Co.* 9:1-3, 1948.

wrestle with the more difficult problems of conserving life and health in the middle-aged and older people. The major concern should be with the cardiovascular-renal diseases, cancer and diabetes since the greatest amount of ill health is due to these conditions. There are a number of other causes of sickness and death among older people that he believes should merit greater attention; these include tuberculosis, pneumonia, mental diseases, nutritional diseases and accidents. Dr. Dublin suggests that the efforts of health departments, private physicians and organized medical groups and voluntary health and safety agencies should be co-ordinated at the local level. The person most suited to take the primary responsibility of co-ordinating these efforts is the health officer, who should be the logical leader in developing effective health service for his community.

PR

PUBLIC relations and the practice of medicine have practically always been nearly synonymous, although their affinity had not been officially recognized until the term "public relations" was recently popularized. The invention of the term and the recognition of its importance have resulted from modern attempts at the orderly organization of all human activities where one group of persons has dealings with another.

Then it was discovered that the old personal relations of the physician with his public were suffering considerably from neglect on both sides and that attempts at repair must be made forthwith.

Certainly considerable elements of the public that have never known and consequently could scarcely appreciate the relations between the good family physician and his practice have found that they did not know how to obtain satisfactory medical advice. Too many physicians have been unconscious of or indifferent to the cordial and reciprocal relations that may and should exist between physician and patient. It is unfortunate but consistent with modern methods that repairs must be made on an assembly-line pattern.

As a result of this growing need in a world where each man looks askance at his neighbor the first national medical public relations conference ever to be held will meet in St. Louis on November 27 to tackle six common objectives confronting the medical profession. The conference is under the sponsorship of the Secretary's office of the American Medical Association, its theme is "Shooting at Common Targets in Medical Public Relations," and qualified speakers will talk on such subjects as "The Public Speaks on Health," "What Public Relations Did for Us," and "Yes, the Profession needs PR."

The six major social issues that will be tackled are: selling the need of public relations to state-medical-society members; encouraging wider use of medical prepayment plans; setting up workable systems for handling night calls; the rebate problem; developing good will with labor, farm, industrial and co-op groups; and co-operating with health agencies.

If, out of the expected welter of slogans, catch phrases, maxims, speech making and general escape of steam in all directions can come the idea that man, and particularly the physician, is after all his brother's keeper, much good will come of the conference.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

APPEL — Bernard H. Appel, M.D., of Brighton, died on September 3. He was in his fiftieth year.

Dr. Appel received his degree from Tufts College Medical School in 1922. He was associate visiting physician at Beth Israel Hospital.

His widow, a son and a daughter survive.

DENNY — Francis P. Denny, M.D., of Brookline, died on September 6. He was in his eightieth year.

Dr. Denny received his degree from Harvard Medical School in 1895. He was chairman of the Advisory Council of Public Health and formerly health director in New London, New Hampshire, and was a member of the New England Pediatric Society and a fellow of the American Medical Association.

His widow survives.

MYERSON — Abraham Myerson, M.D., of Brookline, died on September 3. He was in his sixty-seventh year.

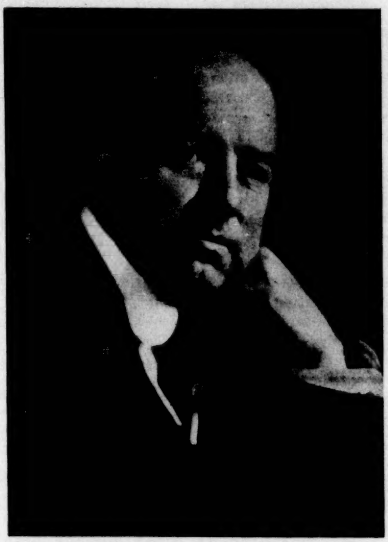
Dr. Myerson received his degree from Tufts College Medical School in 1908. He was professor emeritus of neurology at Tufts College Medical School and formerly clinical professor of psychiatry at Harvard Medical School. He was director of research at Boston State Hospital and was a member of the American Neurological Association, American Psychiatric Association, New England Society of Psychiatry and American Psychopathological Association and a fellow of the American Medical Association.

His widow, two sons and a daughter survive.

RICHARD PEARSON STRONG

(1872–1948)

Richard Pearson Strong was born at Fortress Monroe, Virginia, the son of Colonel Richard Pearson Strong. Throughout his life he exemplified the Army tradition of devotion to duty; whatever he undertook was carried through to the best of his ability. He was never discouraged by difficulties, and he never spared himself when his services were needed, the pre-eminent success of his medical career being due in large measure to these qualities. They were supplemented, however, by good basic training as a member of the first medical class to graduate from Johns Hopkins University School of Medicine and by postgraduate work in Berlin.



Strong's career began as a surgeon in the regular Army during the Spanish-American War. He organized medical research for the Army in the Philippine Islands, serving until 1902. Thereafter, until 1913, he directed the Biological Laboratory of the Bureau of Science in Manila. During this period, he personally conducted a series of important studies on dysentery, plague, cholera and other diseases that made him an international figure in the field of tropical medicine. When the terrible epidemic of pneumonic plague swept northern China in the winter of 1911, Strong was the American delegate to the International Plague Conference, which met in Peking. He and his associate, Teague, went into the stricken area to conduct experiments and to perform autopsies, working in unheated rooms during extremely cold weather, where they were exposed to infection of the most deadly character.

Strong was called to Harvard Medical School in 1913 to become its first professor of tropical medicine. He held this position until 1938, when he became professor emeritus.

From time to time, Strong led expeditions to tropical countries to gather data and to study tropical diseases in their natural habitat. Important among these expeditions were those to Peru in 1913, to the Amazon Basin in connection with the Seventh Hamilton Rice Expedition in 1925, to Liberia and the Belgian Congo in 1926 and 1927, to Guatemala in 1931 and 1932 and again to the Belgian Congo in 1934.

So great was the demand for Strong's services that he was repeatedly granted leave of absence from his University duties. He combated the epidemic of typhus fever that raged in Serbia in 1915; he demonstrated the mode of transmission of trench fever during World War I; he organized the Cannes Conference for the Red Cross in 1919 and assumed leadership of the medical section of the League of Red Cross Societies in Geneva in 1919 and 1920.

After retirement from his professorship at Harvard and at the request of his old friend Admiral Stitt, Strong largely rewrote Stitt's textbook on tropical diseases.

The United States had scarcely entered World War II when Strong was called upon to organize and conduct teaching in tropical medicine at the Army Medical School in Washington. Class after class passed through his hands at intervals of six weeks until the war was over. The acclaim that he received for this teaching and the affectionate admiration that he inspired in the hearts of those who took the courses and in his associates as well testify to the excellence and the value of his contribution. This Washington assignment may be considered as the crowning achievement of his career.

Dr. Strong received many honors from the United States Government, from medical institutions, and from other scientific bodies and universities in the United States, as well as from foreign governments. He died on July 4, 1948, after a protracted and painful illness. His courage and sweetness while in pain were an inspiration to those who were privileged to see him during this period. He will live long in the hearts of his many devoted friends, and his influence will outlive them all.

G. C. S.

BOSTON MEDICAL LIBRARY

IMPORTANT REFERENCE WORKS

The Library, aware of its responsibility to the medical profession of Massachusetts and northern New England, is particularly interested in procuring large or expensive reference works and especially the collected works of famous physicians. In this connection the following works have recently been acquired:

Traité de médecine. Paris, 1948-1949. To be published in seventeen volumes. Eight volumes have been issued to date, covering the subjects of infectious diseases, avitaminoses, intoxications and anaphylaxis, respiratory diseases, diseases of the digestive tract, liver and pancreas and the endocrine glands.

Curry, Manfred. *Bioklimatik. Die Steuerung des gesunden und kranken Organismus durch die Atmosphäre.* Two volumes. Riederau, 1946. This is a monumental work on the relation of climate and weather to man in health and disease.

Gradwohl, R. B. H. *Clinical Laboratory Methods and Diagnosis.* Fourth edition. Three volumes. St. Louis, 1948. This new edition has been greatly expanded. Volume III comprises the material on the subjects of parasitology and tropical medicine. The previous edition was issued in two volumes.

Fuchs, Adalbert. *Die Erkrankungen des Augenhintergrundes.* Wien, 1943. Illustrated with forty-four excellent color plates.

Freud, Sigmund. *Gesammelte Schriften.* Eleven volumes. Leipzig, 1925-1928. The collected works of this important pioneer in psychoanalysis.

Purkyne, Jan Evangelista. *Sebrane spisy.* Four volumes. Prague, 1919-1941. The collected works of a famous physiologist noted for his work on ophthalmoscopy. He made observations on the interior and background of the eye at least twenty-five years before Helmholtz.

NOTE

The Library has recently received a handsome English grandfather's clock from the executors of Mrs. Mary Fifield King. It was presented to the Library in 1897 by Mrs. William B. C. Fifield after the death of Dr. Fifield but was to remain in the possession of Mrs. King as long as she desired. The clock was constructed by Henry Thornton, of London, a member of the Clock Makers Company, in 1699. The date of manufacture was about 1700. After cleaning it will be placed in or near the Fifield Room.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The October schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Lowell	October 1	Albert H. Brewster
Salem	October 4	Paul W. Hugenberger
Haverhill	October 6	William T. Green
Greenfield	October 11	Charles L. Sturdevant
Brockton	October 14	George W. Van Gorder
Worcester	October 15	John W. O'Meara
Gardner	October 19	Carter R. Rowe
Springfield	October 19	Garry deN. Hough, Jr.
Pittsfield	October 20	Frank A. Slowick
Fall River	October 25	David S. Grice
Hyannis	October 28	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

GRAFTON STATE HOSPITAL

Dr. Harlan L. Paine resigned his position as superintendent of the Grafton State Hospital on September 15, 1948, after completing 27 years' service on that date. He will assume the superintendency of the Channing Sanitarium, Inc., in Wellesley, Massachusetts.

QUALIFICATIONS FOR SPECIALIST'S RATING IN PREVENTIVE MEDICINE

Applications from medical officers of the armed forces who want to be certified as specialists in preventive medicine may now be submitted to the Interim Board of Preventive Medicine, according to Department of the Army Circular No. 234, dated August 5, 1948. The circular also outlines the qualifications required of applicants and lists the items to be included in the applications. Written and oral examinations will be held during the fall of 1948 or the spring of 1949.

The circular also announces that the first group of officers to be certified will include those selected by the board as having "considerable experience and a long record of distinguished service in responsible preventive medicine or public health positions." For this first group, formal training and supervised experience requirements, as well as written examination, will be waived.

Examinations and certification will be administered by the Interim Board of Preventive Medicine, formed early this year by joint action of the Surgeons General of the Army, Navy and United States Public Health Service in anticipation of the formation of an American Specialty Board in this field by the Advisory Board for Medical Specialties of the American Medical Association. The Interim Board was set up to serve only the three services.

Prerequisite qualifications include, among other things, membership in the American Medical Association, graduation from a medical school and internship in a hospital approved by the Council of Medical Education and Hospitals of the American Medical Association or by the Army or Navy, the degree of Master of Public Health or its equivalent, and both supervised experience and experience in a position of responsibility in the field of public health or preventive medicine.

CORRESPONDENCE

DRUGS IN HYPERTHYROIDISM

To the Editor: An alarming statement subject to considerable unfavorable notoriety is made in an editorial in the August 5 issue of the *Journal* entitled "The Thyroid Nodule." This statement is quoted in its entirety: "There is also the possibility that the drugs used in the treatment of hyperthyroidism may in some cases precipitate the development of carcinoma."

In view of the large number of patients who are receiving medical treatment of the thyroid gland, either definitively or preoperatively, this statement has widespread implications and deserves amplification and verification. If there is supportive evidence that certain drugs used in thyroid therapy are carcinogenic, they should be specifically mentioned. This type of aspersion may create unnecessary alarm for both patients and physicians and should be either adequately explained or withdrawn.

SEYMOUR B. LONDON, M.D.
ROSE E. LONDON, M.D.

Miami Beach 39, Florida

NOTE: Payne, Crane and Price, in a study entitled "Thiouracil and Carcinoma of the Thyroid" (*Surgery* **22:** 496-501, 1947), reported a carcinoma of the thyroid gland developing in a patient receiving thiouracil in preparation for operation for hyperthyroidism. In unpublished data Bowler presents a similar case. Broders and Parkhill, in an article entitled "Diffuse and Adenomatous Goiter and Goiter Induced by Various Agents" (*Surgery* **16:**633-646, 1944), describe the histology of thiouracil-induced goiters as characterized by cellular hyperplasia with marked mitotic activity, suggestive of carcinoma. In his study on "Tumours of the Thyroid Produced by 2-Acetyl-Amino-Fluorine and Allyl-Thiourea" (*Brit. J. Exper. Path.* **25:**90-95, 1944), Bielschowsky produced thyroid carcinoma in animals by the use of allyl-thiourea in conjunction with the carcinogen 2-acetylamino-fluorine, but was unable to cause thyroid carcinoma by the use of the carcinogen alone. Purves and Griesbach produced thyroid tumors and some cancers in rats treated with thiourea (*Brit. J. Exper. Path.* **27:**294-297, 1946). They stated "We believe that the production of these thyroid tumours is due, not to any direct carcinogenic action of the thiourea administered, but rather to the excessive and prolonged stimulation of the thyroid epithelium . . . ."

It is evident that thiourea derivatives result in extensive hyperplasia with mitoses in man as well as in experimental animals. In animals, adenomas arise as a result of the hyperplasias, as pointed out by Hellwig in a study entitled "Thyroid Adenoma in Experimental Animals" (*Am. J. Cancer* **23:**550-555, 1935). The relation of adenomas to carcinoma development is rather widely accepted. — ED.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Progress in Clinical Medicine. By various authors. Edited by Raymond Daley, M.A., M.D. (Camb.), M.R.C.P.; and Henry G. Miller, M.D. (Durh.), M.R.C.P., D.P.M. 8°, cloth, 356 pp., with 22 illustrations and 15 plates. New York: Grune and Stratton, 1948. $6.00.

Twelve specialists in their particular fields have collaborated in writing this report of progress in certain clinical subjects. The subjects discussed comprise the control of infections, venereal diseases, tropical medicine, gastrointestinal disorders, including liver diseases, metabolic disorders, cardiovascular and renal diseases, blood diseases, diseases of the chest and nervous system, endocrine disorders, psychosomatic medicine and chronic rheumatism. Each subject is documented with a list of selected references. A good index concludes the volume. The printing and type are good. The heavy, coated paper is unnecessary since all plates are inserts. The glare from the paper is distressing and fatiguing to the eyes. The book is recommended for all medical libraries as a reference source.

Foundations of Neuropsychiatry. By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, and psychiatrist in chief, Massachusetts General Hospital. Fourth revised and enlarged edition of the work formerly known as *A Preface to Nervous Disease*. 8°, cloth, 260 pp. Baltimore: The Williams and Wilkins Company, 1948. $2.50.

In this fourth edition of a popular standard manual, first published in 1936 and largely amplified in succeeding editions, the author has made corrections in all sections to keep the text up to date, and new references have been added where considered pertinent. The manual is written for students and practitioners with the object of giving the facts and correlations needed to understand the simpler workings of the central nervous system. The book is well published and is recommended for all medical libraries.

A Synopsis of Anesthesia. By J. Alfred Lee, M.R.C.S., L.R.C.P., M.M.S.A., D.A., consultant anesthetist to Southend General Hospital and Southend Municipal Hospital, Rochford, anesthetist to Tilbury Hospital, Runwell Hospital, East Ham Memorial Hospital and Essex County Council; assistant anesthetist to King George Hospital, Ilford. 12°, cloth, 254 pp., with 42 illustrations. Baltimore: The Williams and Wilkins Company, 1947. $4.00.

This small manual, written for the student, the resident anesthetist and the general practitioner, is a summary of current teaching and practice, and is not intended to displace the large works on the subject. The text covers the whole field of anesthesia and is well arranged. A short first chapter is devoted to notes on history, including a chronology of important dates from 1771 to 1940. The text was printed in England and the sheets bound in the United States. The work reflects the best English practice. It should be in all anesthesia collections.

The Aseptic Treatment of Wounds. By Carl W. Walter, M.D., assistant professor of surgery, Harvard Medical School, and senior associate in surgery, Peter Bent Brigham Hospital. 4°, cloth, 372 pp., with 255 illustrations by Mildred B. Codding, A.M., surgical artist, Peter Bent Brigham Hospital. New York: The Macmillan Company, 1948. $9.00.

This monograph has been written primarily as a text for medical-school courses in surgical technic, but it should prove valuable to operating-room nurses and attendants, manufacturers and distributors of surgical apparatus and to technologists and craftsmen who have to do with such apparatus. The technic described is that elaborated at the Peter Bent Brigham Hospital at Boston during the past twelve years, and reflects the surgical philosophy of Harvey Cushing and Elliott C. Cutler. The author expresses the thought that because of the wide use of chemotherapy surgeons are becoming careless and not following a rigid standardized technic so essential to clean wound healing. Therefore, he has attempted to correlate the existing knowledge on the aseptic treatment of wounds for the general benefit of the operating surgeon and his assistants and technicians. The material is well organized, and the text well written. The subjects of disinfection and sterilization in all their aspects are covered thoroughly. There are chapters on chemical and physical destruction of bacteria, air-borne contamination, operating-room technic, preparation of parenteral fluids, blood and plasma facilities, central-supply-room technic, hospital infection of wounds and the control of communicable disease. The illustrations carry a large part of the book and are excellent in their delineation of the points portrayed. The selected references are printed as footnotes to the text. A good index concludes the volume. The printing is well done with an excellent type, on good, light nonglare paper. The book is delightful to read and is a credit to the publisher. It is recommended for all medical-school and nursing-school libraries and to all persons interested in surgery.

Taking the Cure: *The patient's approach to tuberculosis*. By Robert G. Lovell, M.D., University Hospital, University of Michigan, Ann Arbor. 12°, cloth, 93 pp., with illustrations by Donald Gooch. New York: The Macmillan Company, 1948. $2.00.

This small book has been written for the new tuberculosis patient and contains much sensible practical information. There is a chapter on tuberculosis written for the layman who desires medical information about the disease. The book is well published and easy to read. It should be available to patients and their families.

NOTICES

ANNOUNCEMENT

Dr. Richard N. Abbott announces the opening of his office for the practice of pediatrics at 15 Winnemay Street, Natick.

FBI

The Federal Bureau of Investigation announces that the fugitive from justice concerning whom a notice was published in the *Journal* of August 12, 1948, has been apprehended and is now in custody.

SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, Boston, on Thursday, December 2, at 4:00 p.m.

HAMPDEN DISTRICT MEDICAL SOCIETY

The Program Committee of the Hampden District Medical Society has arranged for the following meetings in 1948-1949. On November 30, 1948, at 8:30 p.m., in the Academy of Medicine, Springfield, Dr. Grantley W. Taylor will speak on the subject "Carcinoma of the Breast." On January 25, 1949, at 8:30 p.m., in the Academy of Medicine, Springfield, Dr. John Rock will speak on the subject "A Review of the Sterility Problem." And on April 26, 1949, at 6:00 p.m., in the Hotel Highland, Springfield (dinner meeting), Dr. Douglas T. Davidson will speak on the subject "Convulsive Disorders."

NEW YORK ACADEMY OF MEDICINE

The Twenty-First Graduate Fortnight of the New York Academy of Medicine will be held October 4 through October 15, the subject being "Advances in Therapy." The program includes morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations.

A physician who is not a fellow of the Academy may obtain registration by sending his name and address, accompanied by a check for six dollars, to the New York Academy of Medicine, 2 East 103rd Street, New York 29, New York.

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology will hold practical examinations in San Francisco from March 21-24, in New York City from June 11-15, in St. Louis from October 15-19 and in Boston in December, 1949. A written qualifying test will be held in January, 1949. Applications for the 1950 written qualifying test are now being accepted.

Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a Written Qualifying Test. These tests are held annually in various parts of the United States.

Registration is already closed for the next test to be given in January 1949.

Applications are now being accepted for the 1950 Written Test. They will be considered in order of receipt until the quota is filled.

A supplementary list of diplomates from January, 1948, to January, 1949, will be sent without charge to all purchasers of the Board's *Directory*. This supplementary material is arranged alphabetically and geographically. No biographic material is included.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA

The centennial celebration of the Medical Society of the State of Pennsylvania will be held in Philadelphia from October 3 to 7. The meeting will consist of scientific sessions at the University of Pennsylvania, social gatherings at the Bellevue-Stratford Hotel and clinicopathological conferences.

Further information regarding the program may be obtained from Dr. Walter F. Donaldson, secretary-treasurer, Medical Society of the State of Pennsylvania, 8104 Jenkins Arcade, Pittsburgh 22, Pennsylvania.

VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Provided essays of sufficient merit are presented in competition, the award will be made at the annual meeting of the association, which will be held in Madison, Wisconsin, on May 26, 27 and 28, 1949.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English, and a typewritten double-spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors' Building, Atlanta 3, Georgia, not later than March 15, 1949. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual *Proceedings* of the association. This will not prevent its further publication, however, in any *Journal* selected by the author.

ARMY MEDICAL RESIDENT TRAINING PROGRAM

Applications for the Military Resident Training Program (in Army general hospitals) are currently being received in the Office of the Surgeon General, United States Army. Under this training program any physician who qualifies for and accepts a commission in the Regular Army Medical Corps will be given the opportunity of competing for an approved residency in the field of his choice.

Medical specialty training available for newly commissioned officers under this program is as follows: a limited number of senior residencies in thoracic surgery, orthopedics, pulmonary diseases, pathology, ophthalmology and physical medicine; a limited number of residencies in orthopedics, pathology and physical medicine; a limited number of assistant residencies in obstetrics, urology, thoracic surgery, dermatology and pediatrics; and a substantial number of assistant residencies in anesthesia, general surgery, orthopedics, internal medicine, psychiatry, pathology, ophthalmology, otolaryngology, radiology, physical medicine and clinical physician training. Some of the assistant residencies in urology, general surgery, internal medicine and radiology are available at the Gorgas Hospital, Canal Zone.

Officers who are not selected to enter residency training on January 1 or July 1, 1949, will, if qualified, be furnished a certificate indicating the date on which they will enter approved professional training. The program is designed to ensure that all qualified applicants will be given the opportunity of completing their requirements for certification by an American specialty board.

October 1, 1949, has been established as the deadline for receipt of applications from physicians who are interested in participating in this training program. Complete information and application blanks may be obtained from the Surgeon General, Department of the Army, Washington 25, D. C.

(*Notices concluded on page xv*)